RECENT ADVANCES IN
ORGANIC CHEMISTRY

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WITH AN INTRODUCTION BY

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IN UNIVERSITY COLLEGE, LONDON

THIRD EDITION

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To

MY FATHER AND MOTHER

EXTRACTS FROM THE PREFACE TO THE FIRST EDITION.

In the present volume the Author has aimed at giving a general idea of the researches which have been carried out in Organic Chemistry within the last ten years, but there has been no rigid adherence to this period when it appeared desirable to include earlier investigations. A considerable portion of the material has not previously been collected in volume form; and as far as possible the most recent work in each branch of the subject has been described.

In dealing with Organic Chemistry two courses are open; for we may consider the matter either historically or from the synthetic point of view. In the present volume the second method has been adhered to as far as possible; and when the synthesis of a substance is known, its constitution has been deduced from the method of formation rather than from its decomposition products. The latter, when important, are reserved for consideration after the constitution has been demonstrated. For the sake of clearness, each step in the syntheses has been treated in a separate section, so that at any moment the reader can see exactly how far he has advanced, and can easily refer back to any stage which he may wish to read again.

As no one ever consults a book of this type when they wish to know the boiling-point of a compound, it would have been superfluous in the following pages to give more than the most general account of the physical properties of the

substances mentioned. Full details on the subject are to be found in Beilstein's "Handbuch der organischen Chemie," to which the reader is referred for information on these points.

University College, London,
September, 1908.

EXTRACT FROM THE PREFACE TO THE SECOND EDITION.

When writing the first edition, I tried to bear in mind that science is not a mere collection of data, but is rather a rapidly changing series of hypotheses by means of which we attempt to group the facts with which we are acquainted; and consequently I endeavoured (as one of my reviewers put it, more clearly than I could do) "to illustrate the principles upon which modern chemistry moves—not stands—and to undermine the conservatism which exists in all but strikingly original minds". The reception accorded to the volume showed that this mode of regarding the subject is more general than I had anticipated.

The Sir Donald Currie Laboratories,
The Queen's University of Belfast,
October, 1910.

PREFACE TO THE THIRD EDITION.

When the last edition of this book was published, it was impossible to foresee the rapid advances which have been made during recent years; and consequently in the present version several subjects find a place which were not sufficiently understood to require mention in the second edition. In addition, parts of the earlier work which have survived intact have required large additions in order to bring them up to date; so that it might almost be claimed that the present volume is practically a new work.

So much new ground has been broken since 1900 that it seemed best to delete the historical chapter of the last edition and replace it by an account of the main lines of research during the twentieth century. The polymethylene group has now ceased to be of immediate interest, so that subject also has been omitted; and the same fate has befallen the chapters on quinoles, asymmetric syntheses, and addition reactions. The bibliography has been deleted for various reasons.

The terpene group excites less general attention than it did in earlier times; and the chapters dealing with it have therefore not been expanded. The alkaloids have required revision, and the chapter on them has been recast so as to include a selection of the latest work in this field. This has resulted in the exclusion of several of the older alkaloid syntheses and a certain divergence from the original lines of the chapter; but it is hoped that the presence of the newer work will atone for the loss of the original symmetrical grouping of the material.

The deletion of several chapters has left room for new subjects. Willstätter's researches on chlorophyll and the anthocyanins, the recent processes for the synthesis of rubber,

and some account of the chemistry of arsenic compounds have been inserted. The chapter on triphenylmethyl has been supplemented by one on recent work on divalent nitrogen, etc.

To keep the book in touch with the modern trend towards the chemistry of natural products and substances of physiological interest, a new chapter has been written containing certain theories bearing upon the synthesis of compounds in vegetable and animal organisms.

One error, common to nearly all text-books, has, it is hoped, been avoided in this one. On comparing the average text-book's statements with those in the original papers, one is frequently struck by the manner in which a tentative suggestion in the journal takes on a dogmatic tone when transferred to the text-book; and in this way a wholly erroneous view of the actual facts is put afloat among those who seldom consult the original literature. Such mishaps cannot altogether be avoided, but it is believed that in the present volume a successful effort has been made to approach the spirit of the originals, and I have striven not to force any point beyond its legitimate range.

An attempt has been made to write in a critical spirit, as was done in the two previous issues. It is possible that readers may detect a certain bias against the flood of synthetic material which pours chiefly from the German laboratories. Lest this should be attributed to a reconsideration of the value of German science in the light of the war, it may be mentioned that exactly the same views were expressed in earlier editions; I have seen no reason to modify my opinions on the subject.

I have again to thank my reviewers for helpful suggestions, and also to acknowledge my indebtedness to Professor Collie, F.R.S., Assistant-Professor Smiles, F.R.S., O.B.E., and Dr. A. K. Macbeth for assistance in the preparation of the present edition.

A. W. STEWART.

THE PHYSICAL CHEMISTRY DEPARTMENT,
THE UNIVERSITY OF GLASGOW,
September, 1918.

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INTRODUCTION.

At the present time it is not altogether easy to say on what lines a text-book of Organic Chemistry should be written. To state in the preface that the Author "hopes it will supply a long-felt want" is not always an injudicious method of announcing the Author's belief in the readers of text-books For if the "long-felt want" of the public is to have a re-statement of all the old facts once more, with nothing new, no critical faculty shown, and an obvious lack of evidence that the book can be used to broaden our outlook on other sciences as well as chemistry, then no doubt the desire of the public for the time being is satisfied.

It certainly is to be regretted, however, that so many books on Organic Chemistry are published regardless of the fact that Organic Chemistry is a growing science. If one wants to know about a new piece of country, to obtain a large number of photographs all taken from the same place is obviously a foolish thing to do. Yet book after book on Organic Chemistry is published, covering the same ground, with a fine disregard of the fact that to the pioneers the outlook is constantly changing. A book that has practically nothing new in it except the description of a few more compounds is unnecessary. Fortunately, however, there are some text-books which are not mere narrations of facts, and which do point out, not only what has been done, but what might be accomplished, and which do make the reader think.

At no time, moreover, is a change wanted in the method of writing text-books more than at present. Deluged as we are with unnumbered facts that have often neither expla-

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At no time, moreover, is a change wanted in the method of writing text-books more than at present. Deluged as we are with unnumbered facts that have often neither expla-

nation nor obvious connection with one another, Organic Chemistry has become a vast rubbish heap of puzzling and bewildering compounds. The sanguine chemist expresses a hope that some day, perhaps, a few of these may be useful. All knowledge ought to be useful, even that obtained by the manufacture of the thousands of new substances which are annually produced in chemical laboratories. But where is it to stop? When one looks at Beilstein's "Handbook" or Richter's "Lexicon," or takes up a current volume of any chemical journal, how many of the compounds or the papers are of interest even to the most enthusiastic chemist? The game of permutations and combinations goes on, the chief object apparently being merely to supplement the already existing myriads of laboratory-made organic compounds.

How, out of all this undigested mass, is the writer of a text-book to glean what is of interest or tell what ought to be taken and what left? The result is that many text-books are not much more than abridged chemical dictionaries. The only tax on the reader's mind is to remember as many facts as possible. The text-book is rare that stimulates its reader to ask, Why is this so? or, How does this connect with what has been read elsewhere?

Indeed, it is not inconceivable that a useful text-book might be written on the constitutional formula of a single organic compound; for instance, alcohol. Its manufacture and physical properties would have to be considered. This would necessitate a knowledge of many typical organic compounds, and also of many kinds of reactions. The evidence thus obtained could then be summed up for the purpose of expressing all these facts by the chemical formula. Here the theory of the constitution of organic compounds would have to be dealt with, beginning with the ideas in vogue at the beginning of last century: Berzelius' Electro-chemical Hypothesis, of how the nature of the elements present had the chief influence on the properties of the compound; Dumas' Type-theory, and how he was the first (about 1840) definitely to recognize the arrangement of the atoms in the molecule: how this idea took about a quarter of a century to

get into the text-books; how Frankland, in 1852, started the idea of valency, from which sprang the modern ideas of chemical structure and linking of atoms; how Kekulé first definitely put forward the idea of the quadrivalence of carbon; how Crum Brown, in 1865, suggested the present form of graphic formulæ and pointed out that they were "not to indicate the physical but merely the chemical position of the atoms". All these ideas have more or less centred round alcohol and its derivatives; and any one who carefully had followed the reasoning that led to these various mechanical methods for representing by a chemical formula the molecular structure of organic compounds would be in a position easily to recognize that our present ideas must in future suffer change just as they have done in the past.

Berzelius' ideas were those of a great mind; but in his day narrower theories were necessary for the more detailed development of chemistry. Dumas' Type-theory, on the other hand, was too narrow; it was a very restricted system of classification, and one that led to many false analogies. Up to the present day, the Frankland-Kekulé conceptions of valency and graphic formulæ have held their own, but there are signs that these, too, will have to be modified; physical as well as chemical properties will have to be accounted for.

The present volume should be of great use to students of organic chemistry. The subject-matter is put in an eminently lucid form that enables the reader easily to follow all the arguments, while at the same time his critical faculty is stimulated. The book, moreover, is unlike so many modern text-books in that it is not a mere compilation of facts; several novel theories on organic chemistry are dealt with, theories that up to the present can hardly be said to have assumed definite shape, but which rather point to the paths along which the pioneers of the science are likely to go in the immediate future.

J. NORMAN COLLIE.

CHAPTER I.

ORGANIC CHEMISTRY IN THE TWENTIETH CENTURY.

In the form in which it exists to-day, organic chemistry may be said to take its root in the work of Frankland[1] at the middle of last century. Once the doctrine of the constancy of valency was accepted, the way was open for Couper[2] and Kekulé[3] to bring order into the vast mass of material which had been accumulated in earlier times; while, later, van't Hoff[4] and Le Bel[5] carried the ideas of molecular arrangement out of two dimensions into three and laid the foundation of our present views. Following in the track of these pioneers, the chemists of the latter half of the nineteenth century developed the theoretical side of the subject very rapidly; while, on the other hand, the modern structural formulæ lent to synthetical work a certainty which had previously been unknown.

Despite the Briarean efforts of the synthetic school, it is safe to say that the latter half of the nineteenth century will be regarded as a time when theoretical speculation played the main part in the development of the subject. Of the hundred thousand organic compounds prepared during that time, the majority were still-born and their epitaphs are inscribed in Beilstein's Handbook. Compared with the great clarifying process which laid the basis of our modern views, they weigh but little in the balance.

The new century opened under different auspices. At first it seemed as though the discoveries in electronic physics would

[1] Frankland, *Phil. Trans.*, 1852, **142**, 417.

[2] Couper, *Phil. Mag.*, 1858, iv., **16**, 104.

[3] Kekulé, *Annalen*, 1866, **137**, 129.

[4] van't Hoff, *Voorstell tot uitbreiding der structuur formules in de ruimte* (1874).

[5] Le Bel, *Bull. soc. chim.*, 1874, ii., **22**, 377.

have their reaction upon our structural views; but though several attempts[1] have been made in this region of the subject, organic chemists in general have not welcomed them with anything like whole-hearted encouragement. There is a feeling, apparently, that in abandoning the usual structural formulæ and replacing them by electronic symbols the subject is being complicated instead of simplified; and this feeling, whether it be due to scientific caution or to mere conservatism, has certainly carried the day for the present. It seems probable that the lack of a concrete model has been one of the drawbacks from which the new movement suffered. Structural chemistry and the conception of molecular asymmetry owed more than we can estimate to the fact that they could be illustrated by mechanical devices which rendered them easy of apprehension by the multitude; and it seems possible that, if electronic models could be contrived,[2] their appearance would stimulate the chemical imagination much more rapidly than any mere written efforts can do.

During the last fifty years the flood of synthetic material, principally from the German laboratories, has tended to obscure the genesis of what we still, out of respect for tradition, term organic chemistry. In its early days the science was devoted to the study of compounds produced by natural methods in plants and animals; and it is interesting to find that during the new century a return has been made to the older field. Nor has this return been devoid of results; for it is surprising to find how many subjects of research have been unearthed among the substances which go to build up the animal and vegetable structures.

The twentieth century was hardly begun, when in 1903 Komppa devised a synthesis of camphor, and thus cleared up a problem which had engaged the attention of many investi-

[1] Nelson and Falk, *School of Mines Quarterly*, 1909, **30**, 179; *J. Amer. Chem. Soc.*, 1915, **37**, 274; Nelson, Beans, and Falk, *ibid.*, 1913, **35**, 1810; Falk and Nelson, *ibid.*, 1910, **32**, 1637; 1911, **33**, 1140; Falk, *ibid.*, 1912, **34**, 1041; Noyes, *ibid.*, 1912, **34**, 663; Fry, *ibid.*, 1912, **34**, 664; 1914, **36**, 248, 262, 1035; 1915, **37**, 885; 1916, **38**, 1323, 1327, 1333; *Zeitsch. physikal. Chem.*, 1911, **76**, 385, 398, 591; 1912, **80**, 29; 1913, **82**, 665; 1915, **90**, 458; Stark, *Jahrb. Radioaktiv Elektronik*, 1908, **5**, 124; 1909, **6**, 12; 1912, **9**, 15; *Physikal. Zeitsch.*, 1912, **13**, 585.

[2] Ramsay (*Proc. Roy. Soc.*, 1916, (A), **92**, 451) devised a simple electrical model which may be capable of elaboration.

gators. Later came the work of Perkin and his school in the terpene group which gave a fresh impetus to study in this branch of the subject.

In the alkaloid series great strides have been made, both in determining constitutions and in devising synthetic methods of preparing the natural substances; whilst the examination of plants and the extraction from them of new alkaloids is proceeding apace.

In the carbohydrate group the problem which looms behind most of the modern investigations is the constitution of cellulose; and the work carried out by Cross, Bevan, Purdie, Irvine, and others is leading us gradually towards a solution of that intricate enigma. Cellulose has an extremely complicated structure; and it is only by breaking up its molecule into simpler compounds and then identifying these that we can hope to determine its constitution. The first step in this direction is evidently to obtain and identify readily purifiable carbohydrate derivatives such as methyl ethers, acetyl derivatives, etc. Then by methylating or acetylating cellulose itself previous to breaking it up, it may be possible to recognize among the decomposition products certain well-defined fragments which will permit of guesses being made at the structure of the parent molecule.

The protein structure is also under investigation; and Fischer's work on the polypeptides has thrown light upon some of the problems which face chemists in this field.

Turning to natural pigments, it will be found that the present century has seen a great advance in our knowledge. Kostanecki's researches on the flavone derivatives cleared up the constitutions of many of the natural dyes. Willstätter's work on chlorophyll has given us some insight into the nature of that mysterious substance, though it would be going too far to claim that even yet we know much about the chlorophyll structure; whilst in the field of flower pigments the same investigator has established the general character of the anthocyanins and has practically reduced future work to a stereotyped line.

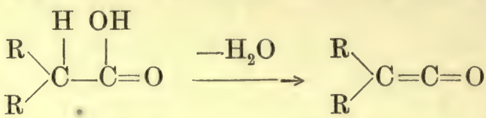
The examination of the colouring matters of the blood and of the bile has opened up yet another branch of pure "organic chemistry"; and the parallelism established between hæmin

and chlorophyll suggests most interesting reflections as to the origin of these two natural substances which play so great a part in animal and vegetable economy.

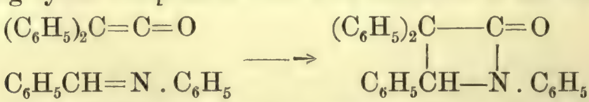
The Anglo-French synthesis of artificial rubber furnishes one of the most striking modern examples of international collaboration, and forms a happy augury for the future.

So much for the results of a return to the original aims of organic chemistry. When the purely synthetic side of the subject is examined in turn, it must be admitted that the results are of less general interest. Of "new" compounds there is no lack; but of "interesting" substances there is a distinct dearth. Two classes, however, stand out with refreshing clearness from the chaotic mass of laboratory by-products: the ketens and the triphenylmethyl derivatives.

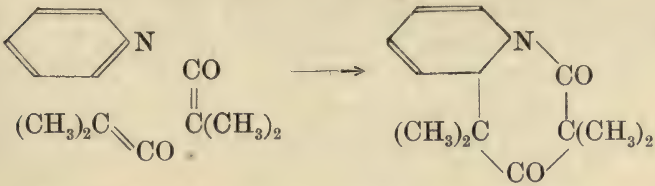
The ketens may be regarded as a new type of anhydride derived from acetic acid or its substitution products :—



In virtue of the ethleno-carbonyl grouping which they contain, the ketens are intensely active and unite with many reagents with the utmost readiness. Thus with water they regenerate the parent acids; with alcohol they yield the corresponding esters; with hydrochloric acid they give the chloro-derivatives of the parent acids; chlorine acts on them to produce chlor-acylchlorides; ammonia yields amides; aniline produces anilides; and on reduction they give aldehydes. Left to themselves, they polymerize with more or less rapidity to tetramethylene derivatives and more complex substances; and they readily oxidize in air. With compounds containing double linkages they combine with more or less readiness, forming cyclic compounds with four members in the ring :—



In the case of certain cyclic bases a similar reaction results in the formation of what have been termed keten bases. Thus with pyridine and dimethyl-keten the product is dimethyl-keten-pyridine :—



The keten class was discovered in 1905 by Staudinger,[1] and the method of preparation devised by him depended upon the removal of two atoms of a halogen from the halide of a halogen substituted acid by means of metals:—

$$R_2 : \underset{\displaystyle |}{\overset{\displaystyle Br}{}}\!\!C—\underset{}{\overset{\displaystyle Br}{|}}\!C : O \xrightarrow{\text{—}2Br} R_2 : C{=}C : O$$

Later, Wilsmore and Stewart[2] showed that the parent substance, keten itself, which had not then been isolated, could be obtained by treating acetic acid or acetone with an electrically heated wire, which removed water in the one case and methane in the second instance.

Though the ketens afford many points of interest, their actual bearing upon theory is not great. The triphenylmethyl and diphenylhydrazyl derivatives, on the other hand, suggest problems which go down to the very root of our ideas of valency. It is perhaps too soon to say that the study of this series will entirely modify our views on chemical affinity; but the progress which has been made since the second edition of this book was printed certainly suggests that the last has not yet been heard of the question.

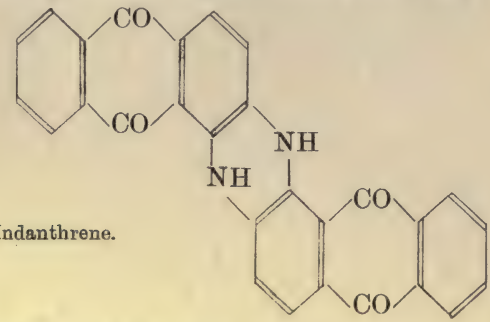
On the technical side organic chemists have not been idle. The great dye industry pours out its flood of colour; and although as a general rule its products have a commercial rather than a scientific interest, two classes deserve notice here.

Vat dyes are those which, like indigo, are almost insoluble in water, but yield on reduction leuco-compounds soluble in alkali. The actual dyeing process is carried out by impregnating the fabric with the leuco-compound and then allowing or forcing oxidation to take place. The earliest example of

[1] Staudinger, *Ber.*, 1905, **38**, 1735.

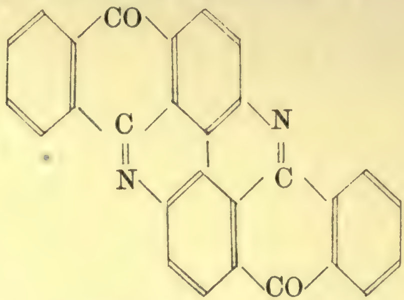
[2] Wilsmore and Stewart, *Nature*, 1907, **75**, 510; Wilsmore, *Trans.*, 1907, **91**, 1938.

the anthraquinone vat dyes, indanthrene, was produced in 1901. It is prepared by fusing 2-amino-anthraquinone with alkali, or by condensing 1-amino-anthraquinone with itself :—



Indanthrene.

To the same class belongs flavanthrene :—



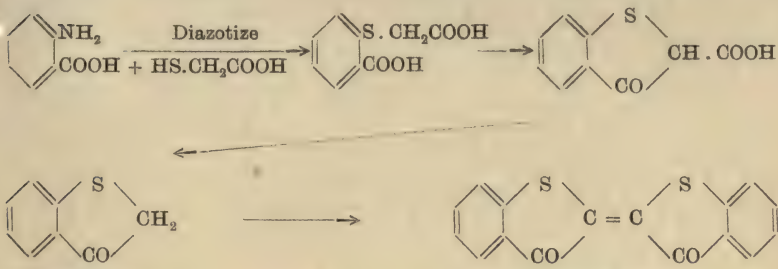
Flavanthrene.

which can be produced by heating 2-amino-anthraquinone with alkali to a temperature higher than that required to form indanthrene. Indanthrene is a valuable dye-stuff of greater stability than indigo; whilst flavanthrene, though giving a blue vat, dyes cotton yellow.

Another class of anthraquinone vat dyes are the acyl derivatives of amino-anthraquinones. For the most part these are yellow or orange in colour, whilst the anthraquinone-imines vary in tint from orange to red or claret colour according to their constitution.

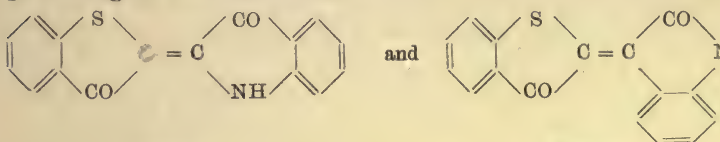
In 1906 Friedländer [1] discovered the thio-analogue of indigo in which the two imino groups are replaced by sulphur atoms; and this substance has become the foundation of a very numerous group of dyes. The following scheme shows one method of synthesis :—

[1] Friedländer, *Ber.*, 1906, **39**, 1060.



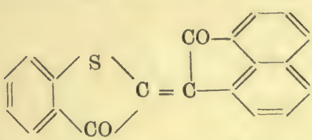
Thio-indoxyl. Thio-indigo.

Thio-indigo imparts a reddish-violet colour to the fabric, and modified tints can be produced by using the amino or halogen derivatives. Further changes in colour are obtained by condensing together one isatin and one thio-indoxyl group, producing mixed structures :—



Violet A. Scarlet.

whilst by uniting thio-indoxyl with diketo-acenaphthenquinone the valuable dye thio-indigo scarlet is obtained :—



Synthetic drugs have been produced in large numbers in recent years. Of these the most important is salvarsan or 606 which is dihydroxy-diamino-arsenobenzene dihydrochloride. It has been used with success to kill the spirochæte which produces syphilis, though, of course, it has no effect in repairing the ravages already caused by the disease if treatment has been delayed. Another organic arsenic derivative employed is atoxyl (also known as arsamin or soamin) which is the mono-sodium salt of *p*-aminophenyl-arsenic acid. It is chiefly utilized in cases of sleeping sickness. Both of these drugs, if used incautiously, may produce blindness.

Numerous new local anæsthetics are now known, such as stovaine, novocaine, and β-eucaine; adrenaline has been

synthesized; and the constituents of ergot are now manufactured for pharmacological purposes.

The modern explosive industry need not be described here, as its newer developments are not yet made public. None the less, it has risen to heights which were not anticipated by anyone before the war.

The new century has already seen the employment of fresh types of reagents; and some account of these must now be given. The most widely applicable of all is that which we owe to Grignard.[1] The rush to apply this new synthetic weapon exceeded anything previously known in the history of organic chemistry; indeed, the original discoverer was left almost out of the race; and hundreds of papers testified to the general eagerness to try the applicability of the magnesium alkyl derivatives to all sorts of problems. Owing to its simplicity and certainty the Grignard reaction stands almost in a class by itself.

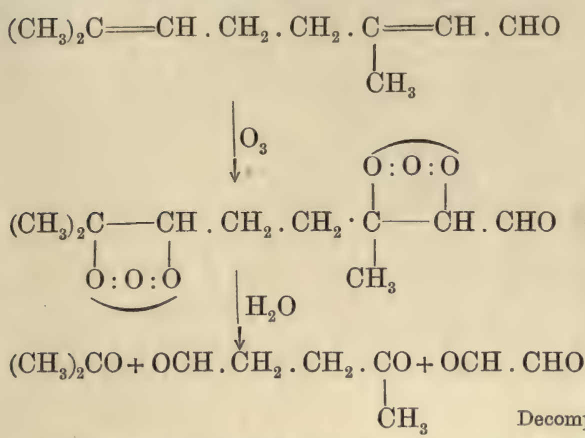
Next to it comes the reduction method of Sabatier and Senderens,[2] which consists in passing a mixture of hydrogen and the substance to be reduced over a heated layer of finely-divided metal. This reaction also has been minutely studied; and the relative catalytic values of various metals have been tested.

A reagent which found wide application in the earlier years of the century is "Caro's acid," prepared by mixing potassium persulphate with concentrated sulphuric acid. The permonosulphuric acid thus formed is one of the most interesting oxidizing agents at our disposal. In general, it is powerful in action; but it may easily be regulated so that the most sensitive intermediate compounds can be isolated, as in the case of the production of nitroso-benzene from aniline.

Ozone is not exactly a new reagent in organic chemistry; but its real usefulness was not recognized until Harries made a thorough examination of its action. It attacks ethylenic linkages and forms ozonides which can be decomposed by water, yielding decomposition products of the original unsaturated compound. The reaction in the case of citral will be sufficient to show the results which are to be expected:—

[1] Grignard, *Compt. rend.*, 1900, **130**, 1322.

[2] Sabatier and Senderens, *Compt. rend.*, 1897, **124**, 616.



Citral.

Citral ozonide.

Decomposition products.

It will be seen that the ozonide method furnishes a means of determining the constitution of ethylenic derivatives; but it must be noted that its application is limited by certain sharply-defined conditions. The ease with which ozone acts upon the particular compound under test, the readiness with which the formed ozonide decomposes,* and the stability of other radicles in the nucleus against attacks by ozone all tend to circumscribe the utility of the reagent.

On the theoretical side of organic chemistry, to which we must now turn, Thiele's views have exerted a considerable influence during the century. It is very seldom that any theory is accepted immediately after being published; usually a considerable time is required during which the chemical world assimilates the author's views in a more or less unconscious manner, until some day they find their way into text-books. It is a remarkable tribute to the value of Thiele's theory that it became a classic almost as soon as it was published.

The Thiele theory [2] is based upon the following assumption: In the case of a double bond between two atoms, it is supposed that the whole of the affinity of the atoms is not used up, but that in addition to the attractive force which is utilized in joining the two atoms together there is a slight excess on each atom. This slight excess of valency Thiele designates by the name *Partial Valency*, and to its presence he attributes the

* The ozonides are explosive substances.

[2] Thiele, *Annalen*, 1899, **306**, 87.

additive power which unsaturated compounds display. To represent the partial valencies, Thiele employs a dotted line, thus—

$$\begin{array}{c} \mathrm{H} \\ \mathrm{R\,.\,C}\ldots\ldots \\ \| \\ \mathrm{R\,.\,C}\ldots\ldots \\ \mathrm{H} \end{array} \qquad\qquad \begin{array}{c} \mathrm{R} \\ \mathrm{R\,.\,C}\ldots\ldots \\ \| \\ \mathrm{O}\ldots\ldots \end{array} \qquad\qquad \begin{array}{c} \mathrm{R\,.\,N}\ldots\ldots \\ \| \\ \mathrm{R\,.\,N}\ldots\ldots \end{array}$$

Now, when we come to the consideration of such a system as

$$\mathrm{R\,.\,CH : CH\,.\,CH : CH\,.\,R}$$

we find that it shows one peculiar property in connection with addition reactions. Since it contains two double bonds, it might be expected to take up four atoms of hydrogen or bromine at once, or at least to take up two atoms of bromine or hydrogen at one of the double bonds. In other words, we should expect to find one molecule of bromine attacking it first with the formation of the compound—

$$\mathrm{R\,.\,CHBr\,.\,CHBr\,.\,CH : CH\,.\,R}$$

to which another bromine molecule might be added, giving the tetrabromo-compound—

$$\mathrm{R\,.\,CHBr\,.\,CHBr\,.\,CHBr\,.\,CHBr\,.\,R}$$

In practice, however, the first molecule of bromine does not attack either of the double bonds; it attacks them both at once, with the formation of the compound—

$$\mathrm{R\,.\,CHBr\,.\,CH : CH\,.\,CHBr\,.\,R}$$

in which both of the original double bonds have disappeared, while a new double bond has been formed in the centre of the molecule. If we write out the scheme of partial valencies for the original substance—

$$\mathrm{R\,.\,\underset{\vdots}{CH} : \underset{\vdots}{CH}\,.\,\underset{\vdots}{CH} : \underset{\vdots}{CH}\,.\,R}$$

it is evident that only the two at the ends of the system have the faculty of attracting bromine, the two middle partial valencies failing to act. In order to express this behaviour Thiele writes the formula in the following way, in which the two central partial valencies are supposed to have neutralized one another :—

$$\mathrm{R{-}\underset{\vdots}{CH}{=}\underbrace{CH{-}CH}{=}\underset{\vdots}{CH}{-}R}$$

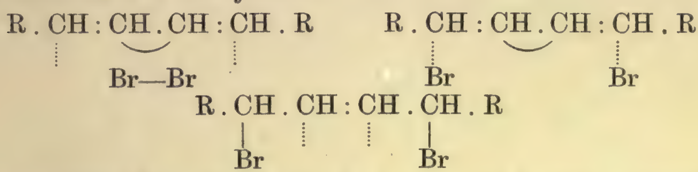
We can make this behaviour clear by supposing that the

carbon atoms of the chain are charged alternately with positive and negative forces, the two central atoms will then neutralize one another, leaving the ends still charged—

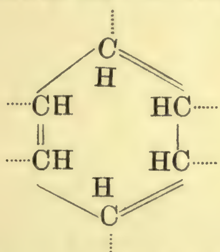
$$R.\overset{+}{CH}:\overset{-}{CH}.\overset{+}{CH}:\overset{-}{CH}.R \qquad R.\overset{+}{CH}:CH.CH:\overset{-}{CH}.R$$

Such a system Thiele terms a *Conjugated Double Bond.*

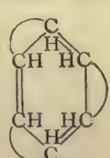
If addition takes place in the case of a conjugated double bond, obviously the two new atoms will attach themselves at the ends of the chain in the position indicated by the free partial valencies. But this does not end the matter: for no sooner has addition taken place than the conjugation is destroyed; and hence a new double bond will be formed between the central atoms of the system—



The most striking application of the Thiele theory, however, is found in the case of the benzene ring. If we write down the Kekulé formula for benzene, and fill in the partial valencies in the usual way, we arrive at the following figure:—

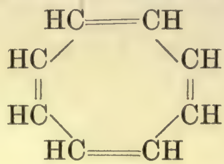


An examination of this system will show that it forms *a closed series of conjugated double bonds.* In other words, it can be written as shown below, and no free partial valencies exist in the system. Hence the impossibility of producing addition products with benzene under ordinary conditions.



Though the theory of partial valencies has very widespread application, it is not absolutely accurate; for several cases are known in which it is not in accordance with the results of experiment.[1]

The benzene problem, which excited so much attention during the latter part of last century, appears to have fallen into the background during the period under review. Collie's dynamic formula,[2] of which all the others which have been suggested are merely phases, is not likely to be displaced, though it may be modified in detail. A point of considerable interest was settled by the synthesis of cyclo-octatetraene.[3]



As can be seen from the formula, this substance contains the same system of alternate single and double bonds which is characteristic of benzene; and it is therefore of interest to know whether or not it is benzenoid in character. Experiment shows that there is no resemblance between its properties and those of benzene; whence it must be deduced that, in order to produce the benzenoid characteristics, the mere alternation of single and double bonds is not sufficient unless reinforced by the presence of six, and only six, atoms in the ring.

As far as the benzene nucleus is concerned, the question which has excited most interest recently is the substitution problem; but it cannot be said that even yet, in spite of extensive investigation, we possess the true key to the riddle.[4]

Passing to other subjects, intramolecular change must be mentioned, as in this region much work of first-class importance has been carried out since the beginning of the century. It would lead us too far were we to enter into any general discussion of the problem; but one or two examples must be given.

[1] Harries, *Annalen*, 1903, **330**, 185; Bredt and Kallen, *ibid.*, **293**, 338.

[2] Collie, *Trans.*, 1897, **71**, 1013.

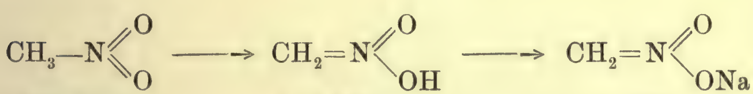
[3] Willstätter and Waser, *Ber.*, 1911, **44**, 3423.

[4] Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (1910); Obermiller, *Die orientierenden Einflüsse und der Benzolkern* (1909).

The most striking of these is the discovery by Hantzsch of a new class of electrolytes which have been named pseudo-acids and pseudo-bases. Previous to his work, the electrolytes known to us might be grouped under the four following heads: (1) Acids, which give rise to hydrogen ions; (2) Bases, which yield hydroxyl ions; (3) Salts, which dissociate into acidic and basic ions; and (4) Amphoteric electrolytes, which are capable of producing either hydrogen or hydroxyl ions according to the experimental conditions employed.

Now when an acid solution is neutralized by means of a base, the solution is acidic at the beginning and remains acidic all through the titration until the neutralization-point is reached. On the other hand, if we start with a solution of nitromethane, it is neutral in reaction; and yet if we slowly add to it a solution of sodium hydroxide, the solution does not become alkaline at once. In fact, we may have to add a considerable quantity of alkali before the next drop produces an alkaline reaction in the liquid. Clearly nitromethane is a neutral substance which, *given time*, can exhibit acidic properties in presence of alkali. It is this *slow neutralization* which distinguishes it from a true acid.

Without going into the details of the evidence,[1] it may be said that intramolecular change is the governing factor in the problem. True nitromethane is not acidic; but in presence of bases it may change into an isomeric body, the *aci*-form, which possesses a hydrogen capable of being replaced by alkali: so that the reaction may be represented by the following scheme :—



Normal form. Aci-form. Salt.

The slowness with which nitromethane neutralizes alkalies is obviously due to the fact that the intramolecular change from the normal to the aci-form is not instantaneous, but requires time for its accomplishment.

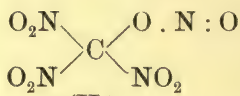
The discovery of the pseudo-acids resulted in the collapse of

[1] For a complete account of the pseudo-acids, see the author's *Recent Advances in Physical and Inorganic Chemistry* (1912).

Ostwald's hypothesis as to the nature of indicators. Ostwald[1] assumed that indicators underwent a change of colour when dissociated into their ions. Thus undissociated phenolphthalein, in his view, was colourless; but when converted into the easily dissociable sodium salt it broke down into ions which were red in colour. By adding acid to the alkaline solution, the dissociation of the phenolphthalein was restricted; and hence the colour disappeared. Stieglitz[2] suggested, on the other hand, that the production of the colour was due to intramolecular change in the phenolphthalein molecule; and Hantzsch[3] confirmed this, showing that phenolphthalein, for example, changes from the benzenoid to the quinonoid structure under the influence of alkali, and on further addition of alkali gives a *colourless* solution, a fact which cannot be explained by Ostwald's hypothesis.[4]

In connection with intramolecular change the case of tetranitromethane may be mentioned.[5] Under normal circumstances, this substance appears to exist in the pure "nitro" form (I.), but in presence of amines or alkyl sulphides it seems slowly to be converted into trinitro-nitrito-methane (II.), as it gives exactly the same colour reactions as are observed in the case of alkyl nitrites:—

(I.)



(II.)

This case seems to be a half-way stage towards pseudo-acid formation.

At this point the progress in stereochemistry during the present century may be conveniently described. It must be confessed that though the period opened with high hopes, these have not been fulfilled by the continuance of interest in the subject; for at the present time it attracts little attention in the chemical world.

[1] Ostwald, *Die wissenschaftlichen Grundlagen der analytischen Chemie* (1894).

[2] Stieglitz, *J. Amer. Chem. Soc.*, 1903, **25**, 112.

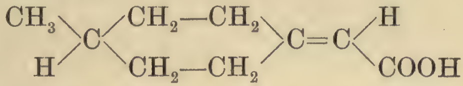
[3] Hantzsch, *Ber.*, 1906, **39**, 1090.

[4] It is perhaps not without interest to note that Ostwald in his *Grundriss der allgemeinen Chemie* (1912) still gives his hypothesis as the correct one—a curious example of incapacity to grasp the bearing of organic problems.

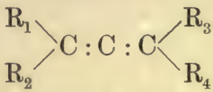
[5] Harper and Macbeth, *Trans.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824.

In 1899 the only two elements known to be capable of forming asymmetric centres of optical activity were carbon and nitrogen; but since then the list has been greatly increased by the addition of sulphur,[1] selenium,[2] tin,[3] silicon,[4] phosphorus,[5] cobalt,[6] chromium,[7] rhodium[8] and iron.[9]

The whole question of molecular asymmetry was raised by a paper of Perkin, Pope, and Wallach[10] describing the resolution into optically active components of an acid having the following structure:—



It will be recalled that in one of his earliest publications on stereochemistry, van't Hoff pointed out that optical activity might be expected in compounds of the type—



owing to the fact that, although there is no asymmetric carbon atom in the molecule, the groups R_1, R_2, R_3, and R_4 are tetrahedrally grouped in space, as can easily be seen by considering the arrangement of bonds around the central carbon atom on the van't Hoff hypothesis. The one double bond lies in the plane of the paper, whilst the other must be at right angles to the paper; and hence a similar grouping of R_1 and R_2 in the plane of the paper and R_3 and R_4 above the plane of the paper must exist. The cyclic compound shown above belongs to the same type, since in its case the ring takes the place of one of the double bonds.

The claim that this substance contained no asymmetric carbon atom was contested[11] on the ground that the carbon

[1] Smiles, *Trans.*, 1900, **77**, 1174; Pope and Peachey, *ibid.*, 1072.

[2] Pope and Neville, *Trans.*, 1900, **81**, 1552.

[3] Pope and Peachy, *Proc.*, 1900, **16**, 42; 116.

[4] Kipping, *Trans.*, 1907, **91**, 209.

[5] Kipping and Challenger, *Trans.*, 1911, **99**, 626; Meisenheimer and Lichtenstadt, *Ber.*, 1911, **44**, 356.

[6] Werner, *Ber.*, 1911, **44**, 1887.

[7] *Ibid.*, 3231.

[8] *Ibid.*, 1912, **45**, 1228.

[9] *Ibid.*, 433.

[10] Perkin, Pope, and Wallach, *Trans.*, 1909, **95**, 1785; compare Perkin and Pope, *Trans.*, 1911, **99**, 1510.

[11] Everest, *Chem. News*, 1909, **100**, 295; *Proc.*, 1911, **27**, 285; Marsh, *Proc.*, 1911, **27**, 317.

atom carrying the methyl group is really asymmetrical if the structure of the rest of the molecule be taken into consideration. The matter seems to be one depending upon the interpretation given to the term "asymmetric carbon atom"; and the reader may form his own judgment on the question.

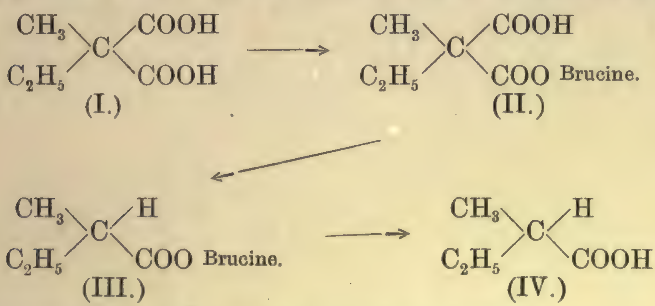
Some new methods of resolving racemic compounds into their antipodes have been devised. Two of these present nothing essentially novel in conception. For example, a racemic base may be treated with an active aldehyde such as helicin and the unsymmetrical product may be separated into two fractions by crystallization, after which, by hydrolysis of the active aldehyde, the required antipode of the base is obtained.[1] Or again, if it be necessary to resolve a racemic ketone or aldehyde, it is combined with an optically active hydrazine, such as menthyl-hydrazine ; the two isomeric hydrazones are separated from one another and then the active compound is regenerated in the usual way.[2]

Much more original was the method devised by Marckwald and Meth[3] which depends upon the difference in rapidity of amide formation between an active amine and the *d*- and *l*-forms of an active acid. Thus if racemic mandelic acid be heated wlth lævo-menthylamine, it is found that the acid left unacted upon after the process had gone on for ten hours was optically active. This method is based on the same line of reasoning as the method of Marckwald and McKenzie[4] who showed that when racemic mandelic acid is esterified with menthol the reaction between the menthol and the *d*-form is more rapid than is the case with the *l*-acid ; so that by interrupting the process before the acid is completely esterified the residual acid is optically active.

A fresh field was opened up by Marckwald[5] in the accomplishment of the first asymmetric synthesis of an optically active substance. In an asymmetric synthesis, an optically active compound is taken as the starting-point. To this an extra radicle is added, so as to form a new asymmetric carbon

[1] Erlenmeyer, jun., *Ber.*, 1903, **36**, 976.
[2] Neuberg, *Ber.*, 1903, **36**, 1192.
[3] Marckwald and Meth, *Ber.*, 1905, **38**, 801.
[4] Marckwald and McKenzie, *Ber.*, 1899, **32**, 2130.
[5] Marckwald, *Ber.*, 1904, **37**, 349, 1368, 4696.

atom. The original optically active portion of the molecule is then split off; and if the synthesis is successful, the remainder of the substance, containing the new asymmetric carbon atom, will be optically active. For example, Marckwald utilized methyl-ethyl-malonic acid (I.) which contains no asymmetric carbon atom. He combined this with optically active brucine, thus introducing asymmetry into the molecule (II.). Now on heating this compound, carbon dioxide is split off forming (III.), a compound which contains a new asymmetric carbon atom. Under the influence of the active brucine, a preference is given to one active form over the other during this process; and when the brucine is split off again, the acid



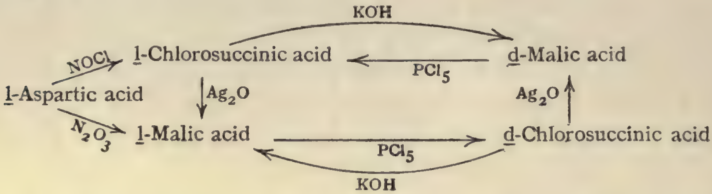
remaining (IV.) is found to be optically active.

In the whole field of stereochemistry, no more puzzling phenomena are known than those grouped under the head of the Walden Inversion; and at the present day we still await a solution of the problem. The data are so complicated that it would be impossible to deal with them fully here: all that can be done is to indicate the nature of the question; and refer the reader for fuller details to the *Annual Reports of the Chemical Society* for the years 1911 and 1912.

Walden[1] observed that when certain optically active compounds were treated with non-asymmetrical reagents the sign of the rotatory power was altered in some cases, dextro compounds being converted into lævo-isomers without any marked racemization being observed. The following scheme shows some of these conversions; and it will be seen that lævo-malic acid, for instance, can be changed into dextro-malic acid

[1] Walden, *Ber.*, 1893, **26**, 213; 1895, **28**, 1287, 2771; 1897, **30**, 3146; 1899, **32**, 1833, 1855.

by the successive use of phosphorus pentachloride and silver oxide; whilst the converse change of dextro-malic acid into the lævo-isomer can be accomplished by the use of the same reagents in the same order:—



Another mysterious case is that of dextro-alanine and its ester.[1] When *d*-alanine is treated with nitrosyl bromide, it produces *l*-*a*-bromopropionic acid; whilst *d*-alanine ester, when subjected to the action of nitrosyl bromide and subsequent hydrolysis, yields the corresponding antipode, *d*-*a*-bromopropionic acid:—

Dextro-alanine $NH_2 . CH(CH_3) . COOH \xrightarrow{NOBr}$ Lævo-*a*-propionic acid.

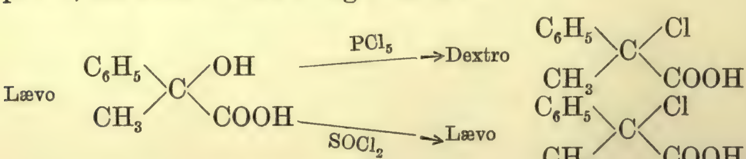
Dextro-alanine ester $NH_2 . CH(CH_3) . COOEt \xrightarrow[\text{hydrolysis}]{\text{NOBr and}}$ Dextro-*a*-propionic acid.

Again, when silver oxide acts upon an *a*-halogen fatty acid and upon the product obtained by coupling this acid with glycine,[2] the results are optically different:—

l-$CH_3 . CHBr . COOH \xrightarrow{Ag_2O}$ d-$CH_3 . CH(OH) . COOH$.

l-$CH_3 . CHBr . CO . NH . CH_2 . COOH \xrightarrow{Ag_2O \text{ and hydrolysis}}$ l-$CH_3 . CH(OH) . COOH$

Finally, the case of *l*-*a*-hydroxy-*a*-phenylpropionic acid may be mentioned.[3] When this substance is treated with phosphorus pentachloride it yields a *d*-chloro-acid; whilst when thionyl chloride is used, there is no change of rotatory power, the *l*-chloro-acid being formed:—



[1] Fischer, *Ber.*, 1907, **40**, 489.
[2] *Ibid.*, 502; Fischer and Raske, *ibid.*, 1052; Fischer and Schoeller, *Annalen*, 1907, **357**, 11.
[3] Mackenzie and Clough, *Trans.*, 1910, **97**, 1016, 2566.

Senter and his collaborators[1] have thrown light upon the matter from a different direction by examining the influence of the solvent on the course of the reaction. In the case of optically active bromophenylacetic acid, $C_6H_5 . CHBr . COOH$, they have shown that if this be allowed to react with ammonia in aqueous or alcoholic solution, the amino-acid formed has a sign opposite to that of the original bromo-compound; whilst if the solvent be liquid ammonia or acetonitrile, the sign of the rotatory power is not reversed by the reaction. Imino-diphenylacetic acid is formed to some extent during the reaction. When *a*-bromo-*β*-phenylpropionic acid, $C_6H_5 . CH_2 . CHBr . COOH$, is treated with ammonia in various solvents, some cinnamic acid is always produced.

To account for the Walden Inversion, Fischer[2] assumes that before a reaction actually occurs, the molecules involved are attracted to one another; and that when a group attached to a carbon atom is replaced by another group, the replacing group does not necessarily take up the position previously occupied by the eliminated group but may, instead, take up another situation in the arrangement round the carbon atom. Thus if the entering group takes up the same position as the eliminated group held, no inversion occurs; but if it takes up a new position, the Walden Inversion is accomplished. The position taken up by the entering group is governed by the nature of the substituting agent and also by the character of the groups attached to the asymmetric carbon atom which is involved in the reaction. Racemization, on this hypothesis, would represent a case in which the forces favouring one position were equally balanced by the forces favouring the other possible situation of the entering group.

Collie[3] regards the matter from a different standpoint. Three factors are apparently involved in the Walden Inversion: (1) the constitution of the optically active compound; (2) the nature of the reagent which acts upon it; and (3) the influence of the solvent in which the reaction is carried out.

With regard to (1), it is clear from the facts given above that the free carboxyl radicle exerts an influence different from

[1] Senter and Drew, *Trans.*, 1915, **107**, 638; 1916, **109**, 1091; Senter and Tucker, *Trans.*, 1918, **113**, 140; Senter, Drew, and Martin, *ibid.*, 151.

[2] Fischer, *Annalen*, 1911, **381**, 123; see also Werner, *Ber.*, 1911, **44**, 873.

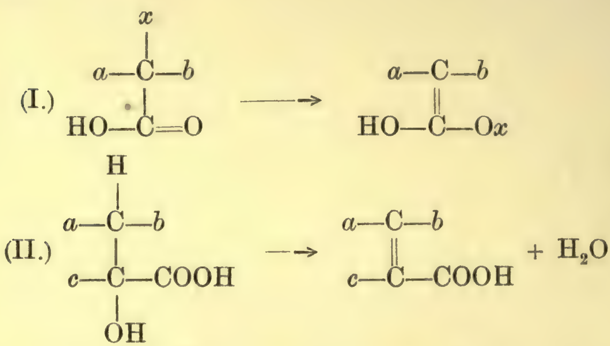
[3] Collie, private communication to the author.

an ester group or an amide radicle. Evidently this implies that the carboxyl group plays some part in the reaction.

The second factor is one which cannot be defined generally, as it depends not only upon the external reagent but also upon the type of optically active material upon which it acts; for a reagent which is powerful in the case of one substance may be weak when applied to another.

The third factor may be considered in connection with the first one, as the solvent may influence the free carboxyl radicle much more strongly than it affects the ester group.

The point of view may be made clearer, as follows. A potential double bond is produced somewhere in the molecule of the optically active compound, either by enolization (I.) or by the abstraction of water, etc. (II.). The addition of the reacting substance can then produce either of the two optical isomers—



In the case of *d*-alanine ester (compare formula (I.) above) the enolization may be assumed to be hindered, and hence no change in configuration occurs in that reaction. Further, when the solvent is one which contains much residual affinity, its affinity will neutralize the affinity of the carbonyl radicle and hence hinder enolization; so that in liquid ammonia solution or solution in acetonitrile, we should expect to find only normal substitution taking place, which is what actually occurs.

The formation of cinnamic acid[1] during the treatment of α-bromo-β-phenylpropionic acid lends experimental support to a conception of this nature, since it proves that the reaction is not one of simple substitution but that, instead, a loss of

[1] Senter, Drew, and Martin, *Trans.*, 1918, **113**, 152.

hydrobromic acid occurs at one stage of the process (compare formula (II.) above).

Again, take the case of *l*-chlorosuccinic acid. When treated with silver oxide it yields *l*-malic acid with no change of sign; but with caustic potash it produces *d*-malic acid. The difference here must obviously be due to the nature of the external reagents. Now silver oxide is a mild reagent, which is unlikely to remove hydrochloric acid from the molecule; and in its case we should expect only a normal substitution. Caustic potash, on the other hand, is a powerful reagent which is often employed to abstract hydrochloric acid. Phosphorus pentachloride also will remove a molecule of water from the optically active hydroxy acid; and the hydrochloric acid formed in the reaction will add itself on to the ethylenic linkage thus formed. If the addition takes place normally, no change in configuration will occur; but if "abnormal" addition takes place, then an acid of opposite rotatory power will be produced.

This explanation has the advantage of bringing together the various phenomena of racemization, asymmetric synthesis, and the Walden Inversion. It also gives a possible explanation of the conversion of active tartaric acid into the meso-form and of dextro-rotatory glucose into lævo-rotatory fructose via the osazone. Moreover, it is merely an extension of the views of Wislicenus on the mechanism involved in the change of maleic into fumaric acid. That decomposition and recombination do occur during the racemization of certain types of compound is evident from the behaviour of some optically active ammonium derivatives.

One of the most complicated problems in the stereochemical field is that which concerns the numerical value of optical rotatory power. Two subsidiary questions are here involved: first, the influence of the active compound's structure; and second, the effect of the solvent in which it may be dissolved. With regard to the first of these we are still apparently far from any satisfactory conclusion, though many facts have been accumulated by various investigators. Certain rough generalizations with regard to the effect of introducing double or triple bonds in place of single linkages have been made; but we are still far from the time when it may be possible to

assess the approximate numerical value of the rotatory power from an examination of the active compound's constitution, as we can do in the case of refractive indices. For our knowledge of the influence which a solvent exerts upon the rotation of an active body in solution, we are chiefly indebted to the lengthy series of investigations carried out by Patterson and his collaborators; and it is possible that ere long a clearer conception of this factor will be gained.

An interesting example of the application of the polarimeter to dynamic problems is furnished by the case of the oximes.[1] When any compound is dissolved in ethyl tartrate, the rotation of the latter substance is affected to a greater or less extent. Patterson and Montgomerie used the labile form of an oxime as their solute; and, since the influences of syn- and anti-oximes upon rotatory power are different, they were able to follow the rate of change from the labile to the stable variety in the polarimeter. Not only so, but by adding an inactive liquid to the solution of the oxime in ethyl tartrate they could measure the influence which this third compound exerted upon the rate of transmutation of the oxime.

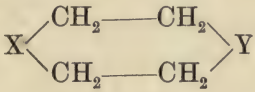
Another problem which has attracted a certain amount of attention in recent times is concerned with what has been termed spatial conjugation. It will be recalled that on the hypothesis of the tetrahedral arrangement of groups around the carbon atom, the first carbon atom in a straight chain may approximate closely in space to the fifth and sixth atoms of the chain. Similarly it is assumed on account of various reactions that the 1 : 4 positions of a six-membered cyclic compound may also be in some way closely related to each other. From an examination of optically active salts and esters of dicarboxylic acids in which the carboxyl radicles lay at opposite ends of the chain, Hilditch[2] showed that when these groups were situated in the 1 : 5 or 1 : 6 positions with regard to one another anomalous rotatory powers were observed; from which it follows that the groups must have influenced one another owing to their proximity in space, since structurally they are far removed from each other.

The same problem was attacked in a different way by

[1] Patterson and Montgomerie, *Trans.*, 1912, **101**, 36, 2100.

[2] Hilditch, *Trans.*, 1909, **95**, 1578.

Clarke.[1] He measured the reactivity of atoms in the positions X and Y in the formula below, wherein X and Y may be = NR, —O— and —S—. All possible combinations of these groups in pairs were investigated:—



It was found that when X and Y are atoms capable of raising their valency (for example: divalent sulphur, which can become quadrivalent, or trivalent nitrogen, which can show pentavalence) and may therefore be supposed to be capable of exhibiting residual affinity, the two atoms X and Y do actually influence each other's reactivities. Further, if X and Y be identical, their reactive power is increased; whereas if X and Y be different (for example X = S and Y = O) their reactivity is diminished.

Another aspect of the question is exhibited when the absorption spectra of stereoisomerides is examined.[2] Since these compounds are structurally identical, the difference in their absorptive power must be ascribed to purely spatial influences. It was found that the difference between the absorption spectra of two isomerides was greatest when the change from one form to the other entailed the relative shifting in space of two unsaturated radicles. When this condition was not present the differences observed were slight.

These pieces of evidence, drawn from such widely differing fields, certainly point to the probability that spatial conjugation is a factor which may play a marked part in certain cases.

We now come to a subject which lies in the borderland between organic and physical chemistry, namely, the relations between the physical properties of compounds and their chemical structure.[3] The problems comprised in this branch have, for the most part, been solved by organic chemists, owing

[1] Clarke, *Trans.*, 1912, **101**, 1788.

[2] Macbeth, Stewart, and Wright, *Trans.*, 1912, **101**, 599.

[3] For a complete account of this field up to 1910, the reader should consult Smiles' *Relations between Chemical Constitution and some Physical Properties.* Even a cursory perusal of the book will suggest many subjects for further investigation.

to the fact that the material of experiment is largely drawn from the carbon compounds. The curious step-motherly fashion in which this important subject has been treated by the ordinary physical chemist is possibly due to the influence of Ostwald, who had a large following among the older group of physical chemists; or it may be ascribed to the fact that few physical chemists have any claim to be ranked as even moderate organic chemists, a fact which handicaps them in this particular line of research. Whatever be the reason, there is no doubt that the relations between chemical constitution and physical properties, so fully recognized by van't Hoff, have not been pursued either with eagerness or success by the physical chemists of the Ostwald school.

Surface tension, specific heat, boiling-point, and melting-point have occupied less attention in recent years. The influence of chemical structure upon viscosity has furnished a subject for a number of workers, among whom Dunstan and his collaborators have been the most successful. The relations between volume and valency have formed the basis of a considerable amount of ingenious speculation by Traube, Barlow and Pope, and Le Bas. The main trend of research, however, has been towards the study of optical properties.

The physical properties of a molecule may be regarded from either of two different standpoints: for we may assume the molecular properties to be merely the sum of the properties of the various atoms in the molecule; or we may decide to lay most weight upon the structural character of the compound. Unfortunately, this mode of classification breaks down at certain points; for it is found that in the case of some substances the properties of the molecule are apparently compounded partly from purely additive factors and partly from constitutive effects. A certain physical property may be traced as an additive factor throughout a whole series of compounds, and then may finally be so greatly influenced by constitutive factors that the value deduced from additive methods diverges widely from the result of experiment upon the next member of the series. Thus when we speak of additive and constitutive properties we mean merely that in the one case the additive factor is predominant, whilst in the second case the influence of constitution outweighs the purely additive effects.

Refractive index gives an example of this. In the case of saturated molecules or unsaturated compounds containing a single centre of residual affinity, the refractivity of the substance can be calculated with extraordinary accuracy by adding together the refractivities of the atoms contained in it. But if the molecule contains a conjugated system * of double bonds such as

$$\text{—CH : CH—CH : CH—} \qquad \text{—CH : CH—}\overset{|}{\text{C}}\text{ : O—}$$

$$\begin{array}{ccc} \text{O} & & \text{N . OH} \\ \| & & \| \\ \text{—C} & \text{——} & \text{CH} \end{array} \qquad\qquad \begin{array}{ccc} \text{O} & & \text{O} \\ \| & & \| \\ \text{—C} & \text{——} & \text{C—} \end{array}$$

the refractivity becomes anomalous and cannot be calculated from the separate refractivities of the atoms. In this case it is clear that constitutive influences are overbearing the purely additive relationship.

Magnetic rotatory power—*i.e.* the power of rotating the plane of polarization which is acquired by symmetrical substances placed in a strong magnetic field—closely resembles refractivity in this respect. Substances containing conjugated double bonds exhibit a certain "exaltation" above the calculated rotatory power; so that here also the influence of the constitutional factor outweighs the additive effects.

Magnetic susceptibility[1] has recently been studied from the constitutional standpoint, and it is found to resemble magnetic rotatory power in character, being influenced partly by additive factors and partly by the general constitution of the molecular structure.

When absorption spectra are examined, it is found that the additive factor is completely overborne, and that the manner in which the atoms are linked together in the molecule exerts far more influence than the nature of the atoms themselves. In recent times this subject has attracted very wide interest, either in the crude form of "relations between colour and constitution" or in the more accurate survey of the visible and ultra-violet regions by the aid of the quartz spectrograph. It would require too much space to deal in detail with the various theories which have been put forward in this branch of the subject; but some idea of the main lines of thought

* See p. 11.

[1] Pascal, *Bull. soc. chim.*, 1909, (iv.), **5**, 1110.

may be given by examining some of the new terminology which has been minted in order to cope with certain problems.

The absorption spectra of simple mono-ketones contain a band in the ultra-violet region. In order to explain the occurrence of this characteristic band, Stewart and Baly[1] assumed that a certain relation existed between the carbonyl group and the hydrogen atoms attached to the neighbouring carbon atom. The exact nature of this relationship may be gathered from a closer consideration of the radicles involved.[2] In the grouping—

$$\begin{array}{ccccccc} & & (1) & & (2) & & \\ R & — & C & — & CH & — & X \\ & & \| & & | & & \\ & & O & & H & & \\ & & & & (3) & & \end{array}$$

it is obvious that the affinity of the carbon atom (1) is occupied in part by the group R, part by the carbon atom (2), and the remainder is devoted to saturating the affinity of the oxygen atom. Similarly, the affinity of the carbon atom (2) is distributed between the group X, the carbon atom (1), and the hydrogen atoms. Without actually postulating that the ketone becomes enolized, it is reasonable to assume that some of the affinity of the oxygen atom and the hydrogen atom (3) must be used up in mutual attraction. Regarded in this way the molecule would represent a closed system, the affinities of whose atoms are mutually saturated. But if we take into account the intramolecular motions of atoms, the case at once assumes a different aspect. It is obvious that the influence exerted by the hydrogen atom (3) upon the oxygen atom will not be constant but will vary according to the distance between those atoms. If we assume, as is usual, that the atoms in a molecule vibrate in closed paths about relatively fixed centres, it is evident that the hydrogen atom will be now approaching, now retreating from the oxygen atom. Every approach will entail a rearrangement of the affinity of the two atoms, and another rearrangement of affinity will take place during their retreat from each other.

[1] Stewart and Baly, *Trans.*, 1906, **89**, 486.

[2] Stewart, *Recent Advances in Organic Chemistry*, 1908, pp. 243-4; *J. pr. Chem.*, 1911, **83**, 194.

According to Stewart and Baly, this fine play of forces within the molecule manifests itself in the production of the ultraviolet absorption band.[*]

Now pyruvic ester, though it contains the same acetyl radicle as a simple ketone, exhibits an absorption band much nearer the red end of the spectrum. To account for this, Stewart and Baly assumed that when two carbonyl groups were adjacent in the molecule a somewhat similar series of affinity-rearrangements occurred, of which the two extreme phases would be represented by—

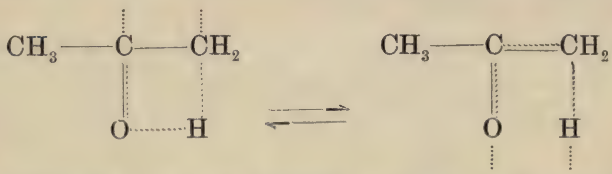
The difference in the nature of the two vibration arrangements in acetone and pyruvic ester accounts for the difference between frequencies at which the absorption bands occur. It must be clearly understood that neither of these phases is supposed to be chemically isolable, any more than the two possible phases of a di-ortho-substituted benzene derivative in the Kekulé formula can be separated from one another. This particular mode of affinity rearrangement between two neighbouring centres (double bonds) was termed "isorropesis". It was extended to the cases of diacetyl benzil and the para-quinones,[2] as an explanation of the colour of these substances.

The isorropesis theory has been attacked by Henderson and Heilbron.[3] To explain the absorption of the simple ketones, they suggest that it is caused by intramolecular vibrations due to the alternate formation and breaking down of unstable ring-systems, the momentary formation of which is effected through the agency of free partial valencies which, under certain conditions, make their appearance on the atoms of the compound. To illustrate their view, they give the case of acetone, which is represented by the following phases :—

* Originally the suggestion was made that there was a direct relation between the persistence of the band and the reactivity of the carbonyl radicle; but recent and more accurate measurements with the spectrophotometer (Rice, *Proc. Roy. Soc.*, 1914, **91**, (A), 76) have disproved this: and it must be regarded as valueless.

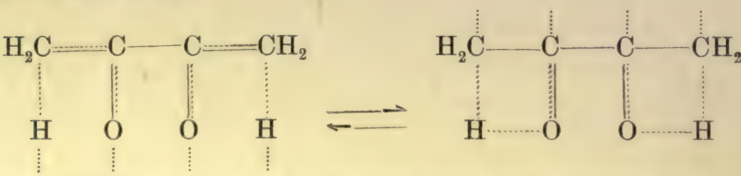
[2] Baly and Stewart, *Trans.*, 1906, **89**, 502.

[3] Henderson and Heilbron, *Proc. Roy. Soc.*, 1914, (A), **89**, 414; Henderson, Henderson and Heilbron, *Ber.*, 1914, **47**, 876.

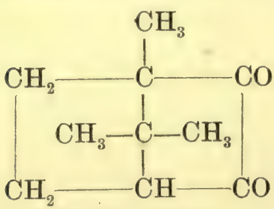


In its essentials this view appears to differ in no way from the earlier suggestions of Stewart and Baly.

In the case of the di-ketones, Henderson and Heilbron reject the type of oscillation termed isorropesis; and regard the colour of the substances as due to the following rearrangement of affinity :—



Unfortunately for this hypothesis, the characteristic band of the *a*-di-ketones is exhibited by certain compounds in which "a double oscillation of the same type as that of acetone" is impossible. Thus camphorquinone, which gives one of the most marked bands of all, contains no hydrogen atom on the carbon atom next one of the carbonyl groups; whilst in the case of benzil, which also exhibits absorption in the same region, there is no hydrogen atom on either of the carbon atoms next the carbonyl radicles :—



Camphorquinone.

$$C_6H_5—CO—CO—C_6H_5$$

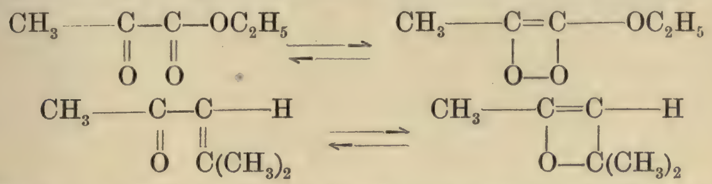
Benzil.

A point of general interest is raised by Henderson and Heilbron in the course of another of their criticisms. They point out that the bands exhibited by pyruvic ester [1] and by mesityl oxide [2] are practically identical; and they conclude from

[1] Stewart and Baly, *Trans.*, 1906, **89**, 489.

[2] Brannigan, Macbeth and Stewart, *Trans.*, 1913, **103**, 406.

this that the isorropesis hypothesis breaks down in this case. It is difficult to see why this should be so, since a similar vibration-structure can be represented in the two molecules in question :—



What seems more important in this case is that the two bands, though they have the same frequency, appear at different dilutions. Looking at the matter from a broad standpoint, it is evident that in any system of vibration there are at least two factors of crucial importance: the periodicity of the vibration—*i.e.*, its frequency—and the amplitude of the vibration. The periodicity determines the wave-length at which the band appears. Clearly the second factor, the amplitude of the vibration, will determine the intensity of the light-absorbing power of the substance.

If this be correct, then substances containing the same general molecular structure—*e.g.*, those in which analogous centres of residual affinity occupy the same relative positions—will exhibit bands of the same frequency ; but their vibrations may differ in amplitude ; and thus the bands may occur at different dilutions. An intramolecular motion which sweeps through a wide arc will involve in a single vibration many more light-waves than a vibration of smaller amplitude can do ; and hence the wide-swinging vibration will extinguish a given light-frequency in a larger number of waves than will be the case with a narrow swing. Thus the dilution at which a band makes its appearance in a solution would, on this hypothesis, be a rough measure of the amplitude of the vibration involved.

The third factor in the character of an absorption band, *viz.*, the range of dilution over which its graph extends, presents yet another problem. Two solutions of the question are possible : for the variation in the depths of bands may be due to purely physical or to chemical causes. The absorptive power of a molecule containing a chromophoric group must be built up from two factors : the banded absorption caused

by the chromophore and the general absorption due to the rest of the molecule. If we alter the non-chromophoric portion of the molecule, we shall alter the general absorptive power also; so that the curves of the general absorption and of the selective absorption will cut in a new point instead of in the original one; and this difference might alter the depth of the band.

This explanation may be extended to include solvent influence in those cases in which the solvent can be supposed to combine chemically with the solute; for in this way we should produce a change in the non-chromophoric portion of the molecule. But there are cases in which it is difficult to assume actual combination between solvent and solute; and yet differences in the absorption spectrum of the solute are observed as we pass from solvent to solvent.[1] A possible explanation is to be found in the fact that pressure appears to exert an influence upon the depths of bands in the absorption spectra of gases.[2] A given quantity of gas at a low pressure is found to have less absorptive power than that shown by the same quantity of gas under high pressure; but the absorption will increase to its original value if a non-absorbing gas be added in a quantity sufficient to give the mixture a pressure equal to the original high pressure. It is possible that the same rule applies in the case of solutions and that each solvent has a specific influence upon the solute, producing upon it a particular pressure-effect; and that the change in the depth of the absorption-band of the solute is to be ascribed to the alteration in pressure as we pass from one solvent to another.

"Halochromism" is a term coined by Baeyer[3] to define the phenomenon of colourless and weakly coloured substances uniting with acids to form strongly coloured salts, although no chromophoric group, in the ordinary sense, is present. For example, dibenzalacetone

$$C_6H_5 . CH : CH . CO . CH : CH . C_6H_5$$

is yellowish in tint; but when dissolved in concentrated sulphuric acid its colour changes to deep orange-red; whilst its solution in strong hydrochloric acid is dark cinnabar-red.

[1] Stewart and Wright, *Ber.*, 1911, **44**, 2819; *Trans.*, 1917, **111**, 183.
[2] R. W. Wood, *Physical Optics*, 1914, p. 444.
[3] Baeyer, *Ber.*, 1902, **35**, 1189; 1905, **38**, 1156.

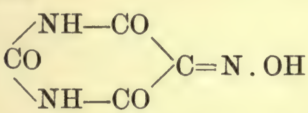
Stobbe proved that the ketone gave a series of compounds with hydrochloric acid which may be represented by the formula (Ketone + x HCl); and he found that at $-75°$ C. $x = 4$, whilst at 15° C. $x = 2$. Other compounds analogous to dibenzalacetone gave similar results, x varying between 1·5 and 5.

From a study of halochromic compounds in the triphenylmethane group, Baeyer was led to suggest that carbon could act as a basic element, giving carbonium salts which were capable of ionizing; and in order to distinguish the "carbonium valency" from the ordinary carbon valency, he indicated the former by a zig-zag line, thus:—

$$(C_6H_5)_3C\sim\!\sim\!\sim Cl.$$

We must now turn to another colour problem. When any salt is formed, it is the general rule that its colour depends upon the colours of the acid and metal from which it is derived. If both of these are colourless, the salt also is usually devoid of colour; if the metallic ion be colourless and the acid be coloured, the salt has a tint similar to that of the acid; whilst in the case of a colourless acid and a metal with a coloured ion, the salt resembles the ion in colour. Such salts are termed by Hantzsch[1] "monochromic".

Cases are known, however, in which salts of the same base and acid occur in differently coloured varieties. Thus the salts of violuric acid:—

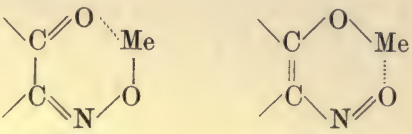


are found to exhibit different tints even when they are derived from colourless metallic ions; for colourless, yellow, red, and violet salts are known to be derived from violuric acid and its derivatives. For example, freshly precipitated silver violurate is almost colourless; but if left in the liquid from which it was precipitated it gradually changes into an apple-green amorphous body, which in its turn is transformed into a crystalline brownish-black salt. Again, violuric acid yields a blue salt with potassium. On crystallizing this from water, a red salt separates along with the blue one. If steam be blown upon the blue salt it is changed to red.

[1] Hantzsch, *Ber.*, 1909, **42**, 967.

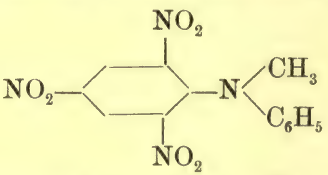
Phenomena such as these are classed by Hantzsch as "polychromism"; and if salts of acids with colourless bases are observed to have a range of colours he defines the case as one of "pantochromism". If a salt changes colour, it is said to be "chromotropic" or "variochromic".

The occurrence of these isomeric salts is explained by Hantzsch as due to "valency-isomerism"; the metallic atom being supposed to be differently attached to the rest of the molecule in each case:—



Chromoisomeric salts.

The matter is made even more complicated by the discovery of certain compounds which, while differing from one another in solubility, melting-point, etc., are indistinguishable from one another either by the spectroscope or the refractometer. Such substances Hantzsch terms "homochromo-isomers". Methyl-phenyl-picramide furnishes an example of this class:—



When synthesized in alcoholic solution from picryl chloride and methyl-aniline, it has m.p. 108° C.; whilst when benzene is used as a solvent instead of alcohol, the compound produced is found to have m.p. 128-9° C. The one form is converted into the higher-melting isomer by crystallization from benzene or by heating to 100° C.; whilst the reverse change is accomplished by allowing the higher-melting isomer to stand at ordinary temperatures or by recrystallizing it from alcohol. Polymorphism has been suggested [1] as an explanation of these phenomena; but Hantzsch [2] asserts that this does not cover the ground.

Another physical property, which appears to be of value

[1] Billmann, *Ber.*, 1910, **43**, 834, 1651, 3153.
[2] Hantzsch, *Ber.*, 1911, **44**, 2007.

in ascertaining the presence or absence of a hydroxyl radicle, is anomalous electric absorption, which was first noticed by Drude.[1] It is found that hydroxylic substances strongly absorb Herzian waves; and this faculty enables enolic forms to be recognized in certain cases.

Electrical double refraction has also been worked upon, but from the results in this case the property appears to be so highly constitutive in character that it varies with very slight changes of structure; so that it is impossible at present to find any way of co-ordinating the numerical results with the chemical side.

The luminescence of certain organic vapours when subjected to the action of a current passing in a solenoid has been studied by Kauffmann in the hope of throwing some light upon the fluorescence problem; but the whole matter of the relation between fluorescence and chemical constitution is still but little understood.

From the foregoing paragraphs it will be seen that an immense amount of research remains to be done upon the connection between physical properties and chemical structure. We still await some general theory which will co-ordinate the various branches of the subject. From a survey of the data at present available, it seems clear that the more purely electrical a property is, the more does the influence of constitution preponderate. Thus refractive index is largely additive; magnetic rotation and magnetic susceptibility are slightly more constitutive in character; anomalous electric absorption and electrical double refraction are almost entirely constitutive properties. It is true that absorption spectra form an apparent exception to this rule.

Photochemistry[2] has grown by leaps and bounds since the beginning of the century and is rapidly reaching the stage when it will be considered a subject in itself. The problems already presented by it are too numerous to be dealt with in this place; and yet the fringe of the subject is all that has been attacked as yet.

The survey given in the previous pages of the progress of

[1] Drude, *Zeitsch. physikal. Chem.*, 1902, **40**, 635; compare Walden, *ibid.*, 1903, **46**, 176.

[2] A full account of the subject is given in Sheppard's *Photochemistry* (1914).

organic chemistry during the present century, though very incomplete, will suffice to indicate the main lines upon which work is proceeding at the present day; and it should be sufficient to show that fresh subjects of research are still plentiful. The newer trend towards a study of natural products comes as a relief after the long supremacy of the purely synthetic work of the late nineteenth century; and it may be emphasized in this place that in the near future the study of quite simple reactions will offer many points of interest. We are far too apt to be captivated by the application of old reactions to new syntheses; and it seems likely that more interesting and useful work could be carried out by an examination of even such obvious problems as the hydration and dehydration of simple organic compounds.

CHAPTER II.

THE MONO-CYCLIC TERPENES.

1. *Introductory.*

WHEN the saps and tissues of certain plants (such as pines, camphor, lemons, and thyme) are distilled, the distillates are found to contain among other things a mixture of substances which are classed under the general head of ethereal oils. For the most part these ethereal oils contain unsaturated hydrocarbons of the general formula $(C_5H_8)_n$ (or derivatives of these substances), and these may be divided into three classes—

1. Open-chain olefinic compounds.
2. Mono-cyclic hydrocarbons (reduced benzene derivatives).
3. Cyclic compounds containing more than one ring.

In the naturally occurring compounds it is found that by far the greater number of these hydrocarbons have the empirical formula $C_{10}H_{16}$; and it is not without interest that Collie,[1] in polymerizing ethylene by means of the silent electric discharge, found that the major part of the substance used was converted into compounds containing either ten or fifteen carbon atoms.

The nomenclature of these substances is at present somewhat in confusion. It has been customary to apply the name terpene to any compound having the composition C_5H_8, or any polymeric variety of this type. This general type was then divided into two others: the "true terpenes," cyclic substances of the formula $C_{10}H_{16}$; and the "olefinic terpenes," which are open-chain bodies having the formulæ C_5H_8 and $C_{10}H_{16}$. Another system of nomenclature classes the whole group under three heads: hemi-terpenes, C_5H_8; terpenes, $C_{10}H_{16}$; and sesquiterpenes, $C_{15}H_{24}$. The naturally occurring mono-cyclic terpenes

[1] Collie, *Trans. Chem. Soc.*, 1905, **87**, 1540.

are for the most part derived from either *m*- or *p*-hexahydrocymene.

Most of the terpenes are colourless, pleasant-smelling liquids of high refractive power. They boil without decomposition, and are volatile in steam. Some are optically active, some inactive by racemization, while others, containing no asymmetric carbon atom, cannot show activity at all.

2. *The Synthesis of Terpineol.*

In the group of the mono-cyclic terpenes, by far the most important compound is terpineol, for from it most of the other members of the group can be prepared, either directly or indirectly. The constitution of terpineol, therefore, is of considerable value to us in determining the constitutions of other substances which we can derive from it. The inactive form of terpineol has been synthesized by Perkin,[1] and as this synthesis determines the constitution of the substance, we may describe it step by step.

When β-iodo-propionic ester was allowed to interact with the disodium derivative of cyan-acetic ester, γ-cyano-pentane-$\alpha\gamma\epsilon$-tricarboxylic ester was produced—

$$\begin{array}{lcl}
 & \mathrm{CN} & \mathrm{EtOOC.CH_2.CH_2\quad CN} \\
 & \diagup & \diagdown\ \diagup \\
2\mathrm{EtOOC.CH_2.CH_2I} + \mathrm{Na_2C} & = 2\mathrm{NaI} + & \mathrm{C} \\
 & \diagdown & \diagup\ \diagdown \\
 & \mathrm{COOEt} & \mathrm{EtOOC.CH_2CH_2\quad COOEt}
\end{array}$$

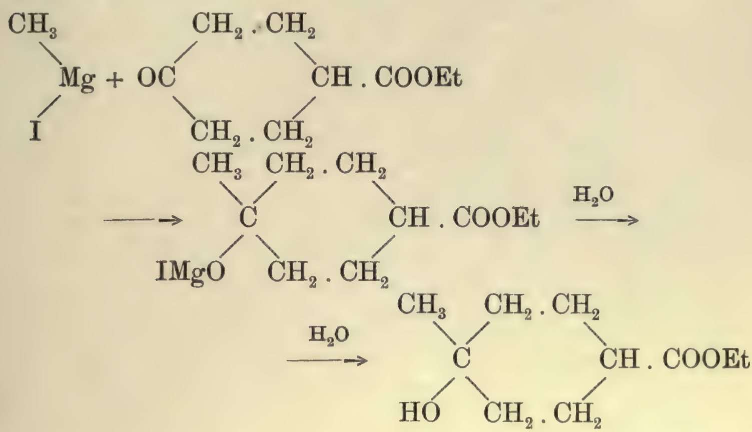
From this the free acid was obtained by hydrolysis with hydrochloric acid, and when it was boiled with acetic anhydride and then distilled, it was transformed by loss of water and carbon dioxide into δ-keto-hexahydrobenzoic acid—

$$\begin{array}{l}
\mathrm{HOOC.CH_2.CH_2} \\
\qquad\qquad\diagdown \\
\qquad\qquad\quad \mathrm{CH.COOH} = \mathrm{H_2O} + \mathrm{CO_2} + \\
\qquad\qquad\diagup \\
\mathrm{HOOC.CH_2.CH_2}
\end{array}$$

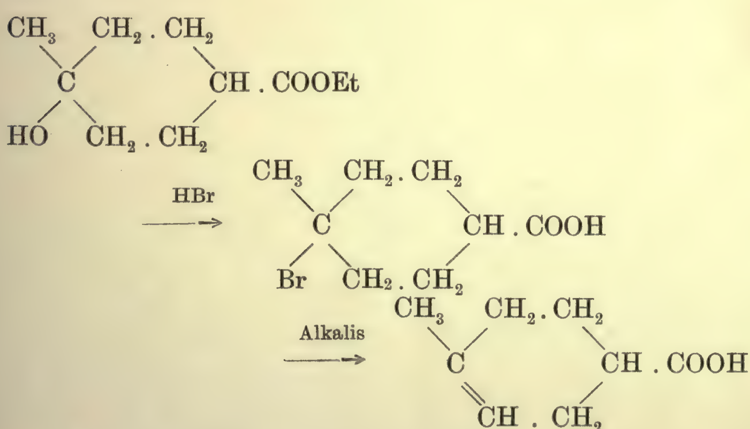
$$\begin{array}{ccccc}
 & & \mathrm{CH_2.CH_2} & & \\
 & \diagup & & \diagdown & \\
+\ \mathrm{CO} & & & & \mathrm{CH.COOH} \\
 & \diagdown & & \diagup & \\
 & & \mathrm{CH_2.CH_2} & &
\end{array}$$

[1] Perkin, *Trans. Chem. Soc.*, 1904, **85**, 64, 5.

Grignard's reaction was then applied to the ester of this acid, magnesium methyl iodide being allowed to react with the ketonic group, and in this way δ-hydroxy-hexahydrotoluic ester was formed—

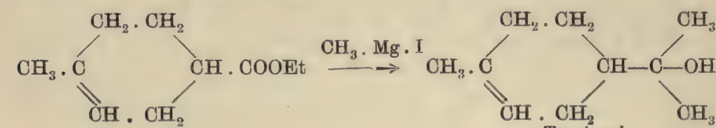


When, by the action of fuming hydrobromic acid, we replace the hydroxyl group in this acid by a bromine atom and then remove hydrobromic acid from the compound by means of weak alkalis or pyridine, we obtain Δ^3-tetrahydro-*p*-toluic acid—



After esterifying the acid, the Grignard reaction can be again employed, with the result that the ester group is attacked,

and on treatment with water the intermediate compound breaks down into inactive terpineol.



Terpineol.

If this synthesis be examined step by step it will be seen that there can be no doubt as to the constitution of terpineol, for the reactions can only be supposed to take place in the way shown. Any alternative formulation of any of the reactions would at once lead to contradiction in the later experiments.

An optically active terpineol has been prepared by Fisher and Perkin [1] by resolving the intermediate acid into dextro and lævo forms before continuing the synthesis.

3. *The Decomposition Products of Terpineol.*

The oxidation of terpineol takes place in several steps and produces some compounds of importance in the study of terpene constitutions; we may, therefore, deal with the matter briefly in this place.

It has been shown by Wagner [2] that when a compound containing a double bond is oxidized by means of potassium permanganate, the first step in the process is the breaking of the double bond and the addition of a hydroxyl group to each of the atoms between which the double bond originally lay—

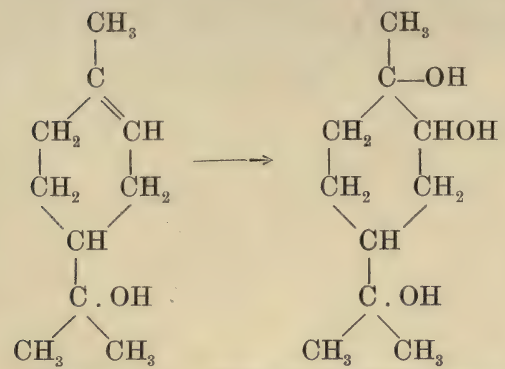
$$\begin{array}{c} \mathrm{R—C—R} \\ \| \\ \mathrm{R—C—R} \end{array} + \mathrm{H_2O} + \mathrm{O} = \begin{array}{c} \mathrm{OH} \\ | \\ \mathrm{R—C—R} \\ | \\ \mathrm{R—C—R} \\ | \\ \mathrm{OH} \end{array}$$

In the case of terpineol this rule holds, and it is found that the first oxidation product [3] obtained by the action of permanganate upon terpineol is trihydroxyhexahydrocymene—

[1] Fisher and Perkin, *Trans. Chem. Soc.*, 1908, **93**, 1871.

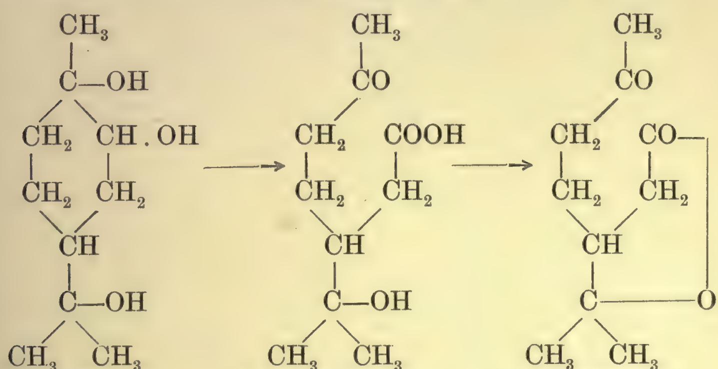
[2] Wagner, *Ber.*, 1888, **21**, 1230, 3359; 1891, **24**, 683.

[3] Wallach, *Annalen*, 1893, **275**, 150.



Terpineol. Trihydroxyhexahydrocymene.

This substance, on further oxidation,[1] is converted into homoterpenylic methyl ketone by the rupture of the single bond between the two hydroxyl-bearing carbon atoms—



Trihydroxyhexahydrocymene. Intermediate acid. Homoterpenylic methyl ketone.

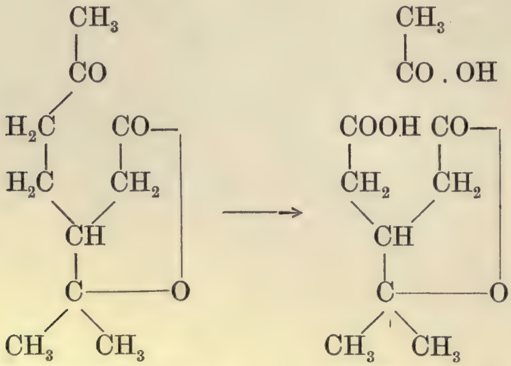
As is shown in the formulæ, the first product of the oxidation is a hydroxy-acid which loses water at once between its carboxyl and hydroxyl groups, yielding the keto-lactone. This keto-lactone is the first product which can be isolated when terpineol is oxidized with chromic acid, for the action is so violent that the trihydroxyhexahydrocymene is destroyed as soon as it is formed.

Further oxidation with potassium permanganate[2] converts

[1] Wallach, *Annalen*, 1893, **275**, 150; *Ber.*, 1895, **28**, 1773; Tiemann and Schmidt, *ibid.*, 1781.

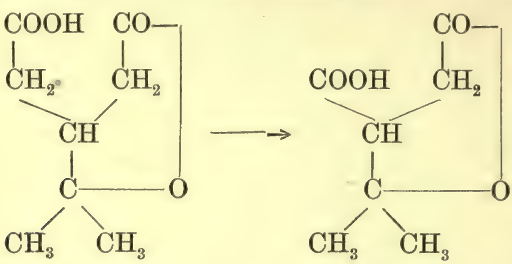
[2] Wallach, *Ber.*, 1895, **28**, 1776.

the keto-lactone into a mixture of acetic and terpenylic acids—



Homoterpenylic methyl ketone. Terpenylic acid.

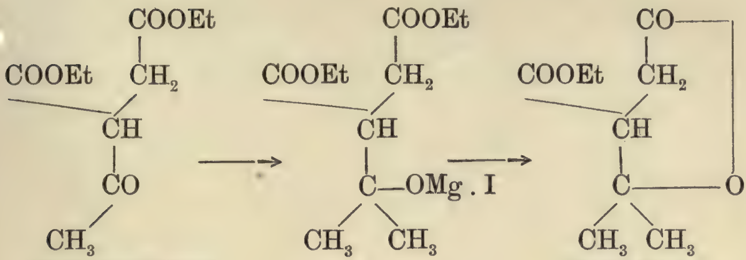
The latter substance, by the action of a 5 per cent. solution of permanganate, is still further decomposed into terebic acid—



Terpenylic acid. Terebic acid.

It will be seen that these formulæ for homoterpenylic, terpenylic, and terebic acid illustrate the decomposition of terpineol quite satisfactorily. Any doubt as to their accuracy was removed by the synthesis of the three acids, which was carried out by Simonsen.[1] Terebic[2] and terpenylic acid[3] had previously been synthesized in different ways. The Simonsen syntheses depend on the application of Grignard's reaction to various ketonic esters. From magnesium methyl iodide and acetyl-succinic ester he obtained terebic ester—

[1] Simonsen, *Trans. Chem. Soc.*, 1907, **91**, 184.
[2] Blaise, *C. R.*, 1898, **126**, 349.
[3] Lawrence, *Trans. Chem. Soc.*, 1899, **75**, 531.



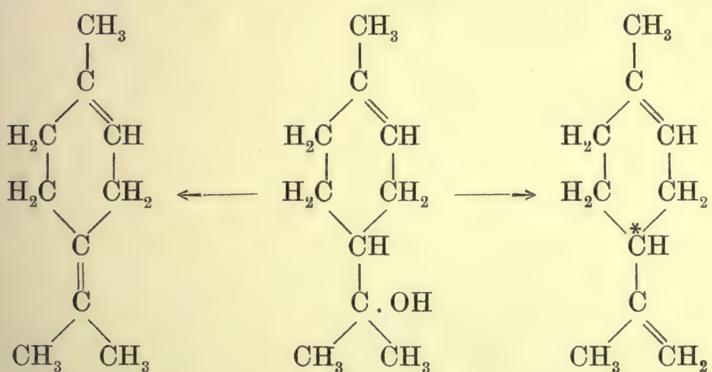
Acetyl-succinic ester. Terebic ester.

In exactly the same way β-acetyl-glutaric ester is converted into terpenylic ester, and β-acetyl-adipic ester into homo-terpenylic ester.

The constitution of terpineol, then, may be considered to be completely established, both synthesis and degradation products agreeing with the theory.

4. *The Constitution of Dipentene.*

When terpineol is heated with acid potassium sulphate it loses a molecule of water, and is converted into dipentene. It is evident that we may represent this elimination of water in either of two ways—

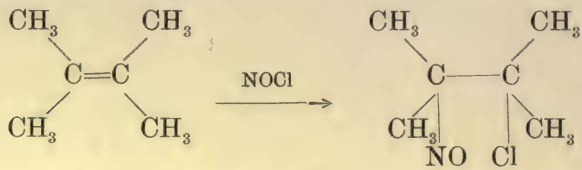


(I.) Terpineol. (II.)

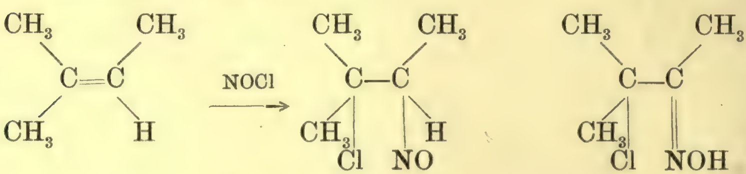
Now, dipentene can be obtained by mixing together equal quantities of dextro- and lævo-limonene. It is, therefore, the racemic form of limonene, and must contain an asymmetric carbon atom. Formula (I.) contains no such carbon atom, but the atom in (II.), which is marked with an asterisk, is asymmetric. Dipentene, then, must have the constitution represented by (II.).

In order to satisfy ourselves that this formula is the correct one, we may test it by seeing how far it agrees with some decompositions which dipentene can be made to undergo.

When nitrosyl chloride is allowed to act upon a compound containing a double bond it may unite with it in either of two ways.[1] If the double bond lies between two tertiary carbon atoms, the chlorine atom attaches itself to the one and the nitroso group to the other, and the resulting substance is a *blue* nitroso-derivative—



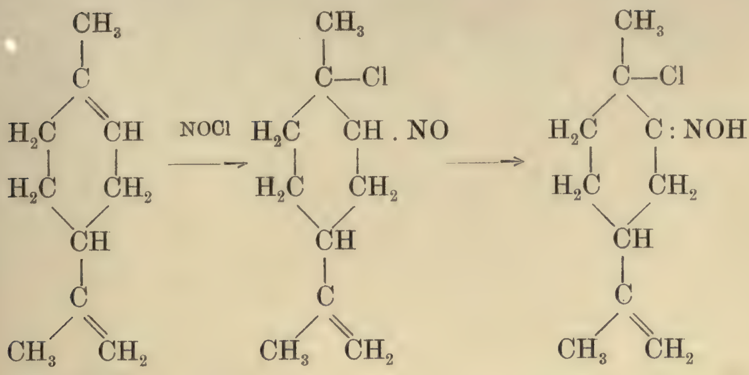
On the other hand, if one of the carbon atoms is a tertiary and the other a secondary one, the chlorine of the nitrosyl chloride attaches itself to the tertiary atom and the nitroso-group to the secondary atom. The hydrogen atom then wanders, as shown in the formulæ below, with the result that a *colourless iso*-nitroso-compound is formed—



We must now apply this to the case of dipentene. To make reference easy we shall number each step.

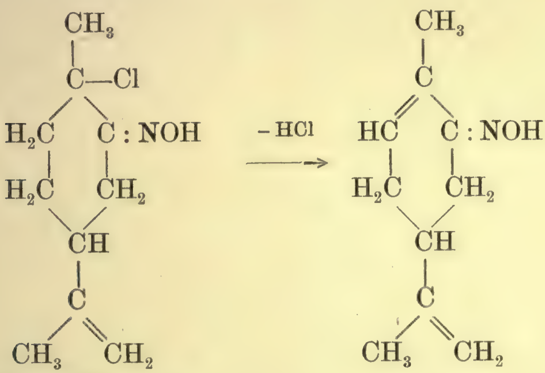
I. When nitrosyl chloride acts upon dipentene, it might be supposed that it could react either with the double bond in the nucleus or with that in the side-chain. It actually attacks the nuclear double bond, as we shall show later, and to avoid the complication of two sets of formulæ we may confine ourselves to the case of the addition to the double bond of the nucleus. The reaction, if our formula for dipentene be correct, will take the course shown below—

[1] Thiele, *Ber.*, 1894, **27**, 455.



Dipentene.

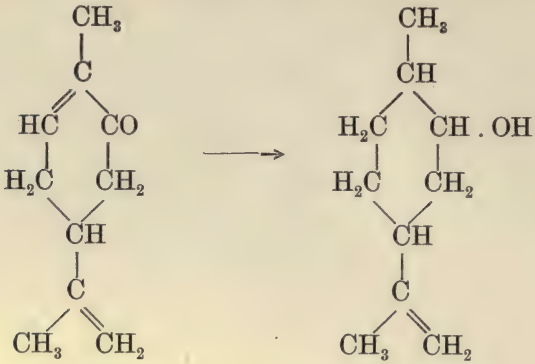
II. When the nitrosochloride formed in the last reaction is treated with alcoholic potash it loses one molecule of hydrochloric acid, and is transformed into a compound which proves to be identical with the oxime of the ketone carvone. This can be expressed as follows :—



Dipentene nitrosochloride. Carvoxime.

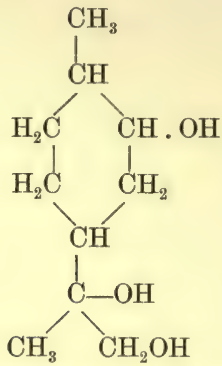
III. By hydrolysis of the oxime, carvone is produced.

IV. Carvone, on reduction, gives dihydrocarveol. This reduction might be supposed to take place either in the nucleus or in the side-chain. As will be shown later (VI.), the nucleus is reduced and the side-chain left untouched. We need not concern ourselves with the alternative set of formulæ, but may again confine ourselves to the one set—

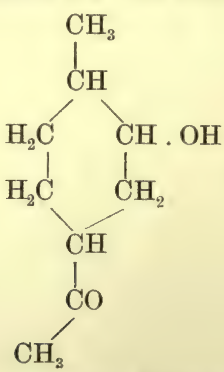


Carvone. Dihydrocarveol.

V. On oxidation, dihydrocarveol gives a trihydroxyhexahydrocymene—

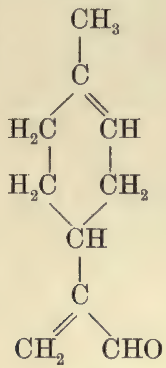


VI. On further oxidation a ketone alcohol is formed—



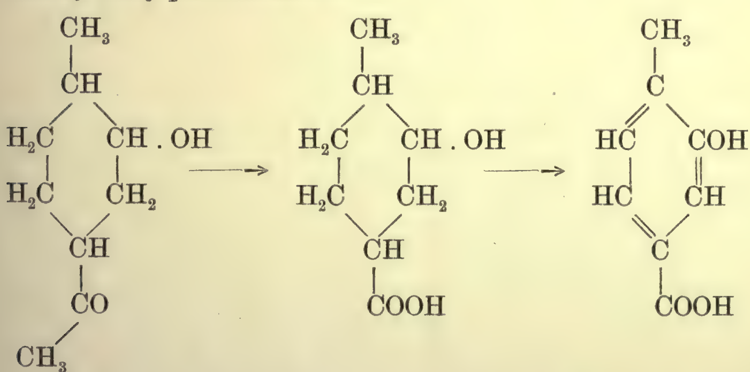
The production of this substance proves what was previously stated in I. and IV., *viz.*, that the nitrosyl chloride attacks

the nucleus, and that in the reduction to dihydrocarveol the side-chain double bond is not reduced. If the nitrosyl chloride had attacked the side-chain we should, at Stage III., have produced an aldehyde of the type—



instead of the ketone produced in practice. If the side-chain had been reduced in Stage IV. instead of the nucleus, the nucleus would have been attacked by the oxidizing agent in Stage V., the ring would have been broken, and a ketonic *acid* would have been formed, just as in the case of the oxidation of terpineol.

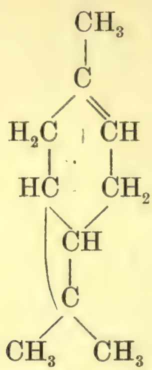
VII. Further oxidation of the ketonic alcohol produced in Stage VI. yields a hydroxy-acid, which, by the action of bromine at 190° C., loses six hydrogen atoms, and is converted into hydroxy-*p*-toluic acid—



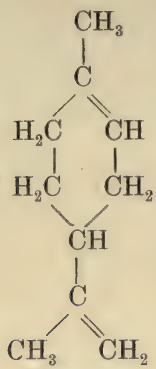
To sum up the matter, we may point out that the series of reactions IV. to VII. prove that the "isopropyl group"

contains a double bond, which must also be present in dipentene. Moreover, since this double bond has persisted throughout the whole series of reactions I. to IV., it cannot have been the point at which the nitrosyl chloride attached itself, as this portion of the molecule has given rise to the —CH . OH— group Further, the nitroso group must have attached itself to the carbon atom to which the hydroxyl group is attached in the aromatic acid, *i.e.*, the one next that which carries the methyl group. These reactions can only be explained by assuming that dipentene has the structure which we attributed to it on account of its synthesis from terpineol.

It might be objected that we have not taken into account the possibility that, in the formation of dipentene, the elimination of water from terpineol may take place between two *non-adjacent* carbon atoms, giving rise to some such compound as—



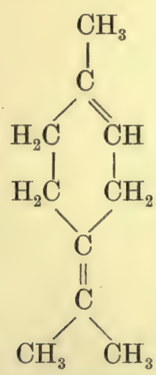
Any attempt to explain the question on these lines leads, however, to impossible results, and it may be taken as proved beyond doubt by the above experimental data that the structure of dipentene is as shown in the annexed formula. This, in turn, proves the formulæ of dextro- and lævo-limonene, for as they are the optical antipodes of which dipentene is the recemic variety, they also must possess the same structural formula as dipentene—



Dipentene.

5. *The Constitutions of Terpinolene and Terpinene.*

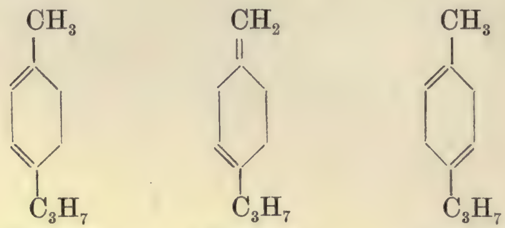
In the last section it was pointed out that the dehydration of terpineol might follow either of two courses: the one leading to a compound containing an asymmetric carbon atom, the other to a symmetrical derivative. The result of dehydration by means of acid potassium sulphate was shown to be dipentene; but when terpineol is dehydrated[1] by means of alcoholic sulphuric acid, an isomeric-compound is formed which has the second of the two possible formulæ. This substance is terpinolene—



When terpinolene is treated with acids, it is converted into a substance which was originally assumed to be a single hydrocarbon terpinene; and for a considerable time the constitution of terpinene was one of the riddles of organic chemistry. From

[1] Wallach, *Ber.*, 1879, **12**, 1022.

the results of his investigations, Wallach[1] deduces that there is no such thing as a pure "terpinene"; but that the material to which this name has been given is a mixture of three different chemical individuals for which he proposes the following names and formulæ:—



α-Terpinene. β-Terpinene. γ-Terpinene.

6. *Terpin and Cineol.*

Grignard[2] and others have shown that when the esters of organic acids react with organo-magnesium compounds, tertiary alcohols can be produced—

$$2R.Mg.I + R'.COOEt = R'.C\begin{matrix}\diagup R \\ -OMg.I \\ \diagdown R\end{matrix} + EtO.Mg.I$$

$$R'.C\begin{matrix}\diagup R \\ -O.Mg.I \\ \diagdown R\end{matrix} + H_2O = R'.C\begin{matrix}\diagup R \\ -OH \\ \diagdown R\end{matrix} + HO.Mg.I$$

Again, when ketones are treated with Grignard's reagent,[3] tertiary alcohols are formed—

$$\begin{matrix} R \\ | \\ CO \\ | \\ R \end{matrix} \xrightarrow{R'.Mg.I} \begin{matrix} R \\ | \\ R'-C-O.Mg.I \\ | \\ R \end{matrix} \xrightarrow{H_2O} \begin{matrix} R \\ | \\ R'-C-OH \\ | \\ R \end{matrix}$$

Kay and Perkin[4] have combined these two reactions into

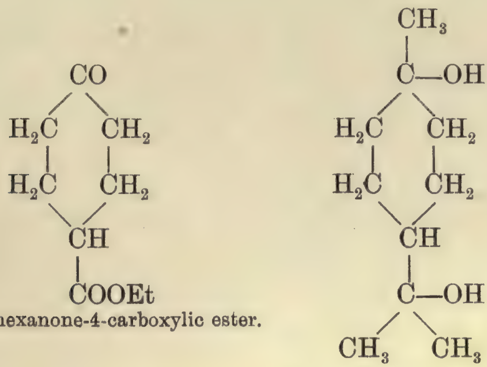
[1] Wallach, *Annalen*, 1910, **374**, 224; 1906, **350**, 142; *Terpene und Campher*, 1906, pp. 467-81.

[2] Grignard, *C. R.*, 1901, **132**, 336.

[3] Zelinsky, *Ber.*, 1901, **36**, 3950.

[4] Kay and Perkin, *Trans. Chem. Soc.*, 1907, **91**, 372.

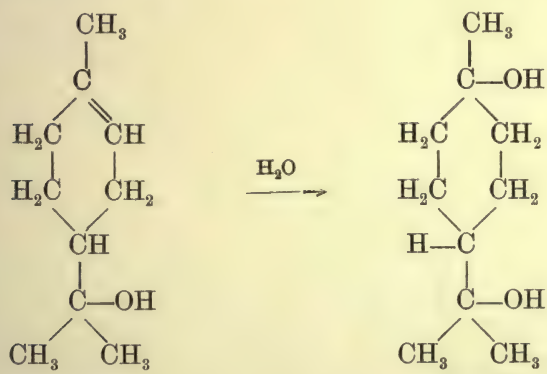
one, using a ketonic ester, and allowing both vulnerable groups to be attacked simultaneously. By this means, from cyclohexanone-4-carboxylic ester, they obtained the dihydric alcohol terpin—



Cyclohexanone-4-carboxylic ester. Terpin.

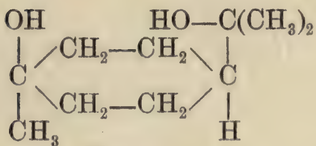
This synthesis proves the formula of terpin beyond any dispute.

Terpin may be also obtained by boiling terpineol with dilute sulphuric acid—

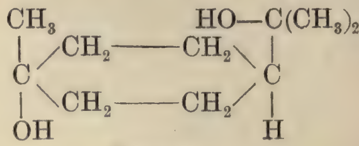


Terpineol. Cis-terpin.

The terpin which is obtained in either of these ways is called *cis*-terpin, from the fact that in its space formula the two hydroxyl groups lie on the same side of the hexamethylene ring, while in the isomeric compound, *trans*-terpin, they lie on opposite sides of the ring—



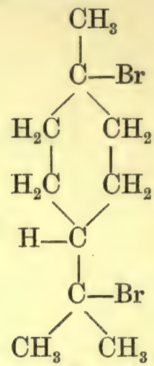
Cis-terpin.



Trans-terpin.

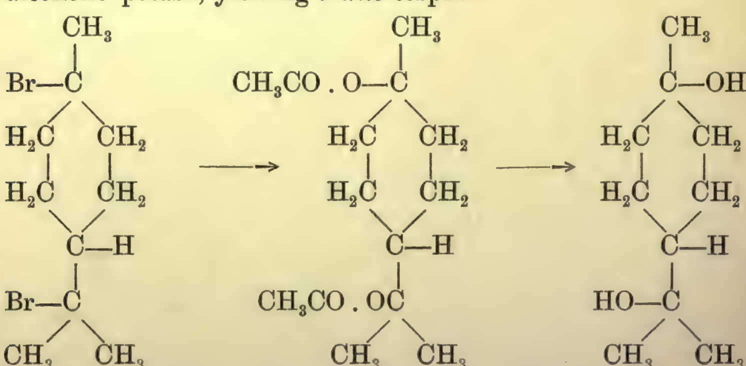
Cis-terpin unites with one molecule of water to form terpin hydrate, a crystalline substance from which it can be regenerated at 100° C. The trans-isomer does not unite with water at all.

Cis-terpin cannot be directly converted into trans-terpin, but the change can be effected by a somewhat roundabout method. In the first place, cis-terpin is subjected to the action of hydrobromic acid, by which means a dibromide is formed. As can be seen from its formula, this substance is identical with the hydrobromide of dipentene—



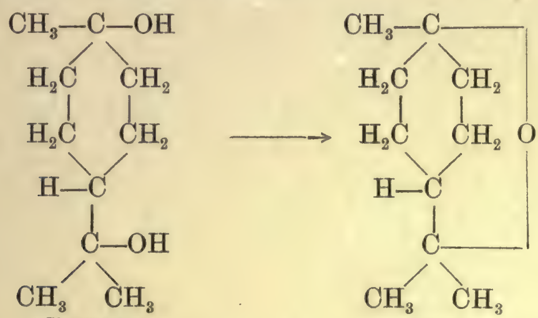
Dipentene dihydrobromide
(Cis-terpin dibromide).

This dibromide is next treated with silver acetate in acetic acid solution, and the diacetate so produced is hydrolyzed with alcoholic potash, yielding *trans*-terpin—



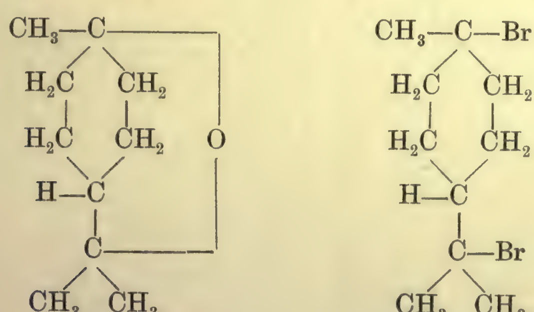
It should be noted that when cis-terpin is converted into its dibromide the product is the *cis*-form of dipentene dihydrobromide; while, on the other hand, the action of hydrobromic acid on trans-terpin produces the *trans*-variety of dipentene dihydrobromide. Thus the change of cis-terpin into trans-terpin cannot be carried out through the bromides alone, as during their formation no change from cis- to trans-form takes place; this only occurs during the hydrolysis of the acetyl derivative.

When cis-terpin is dehydrated, it yields a variety of products (terpineol, dipentene, terpinene, and terpinolene), among which is found the compound cineol, $C_{10}H_{18}O$. This substance contains neither a hydroxyl nor a carbonyl radicle, and must therefore be an ether. On this view, its formation from cis-terpin is easily explained—



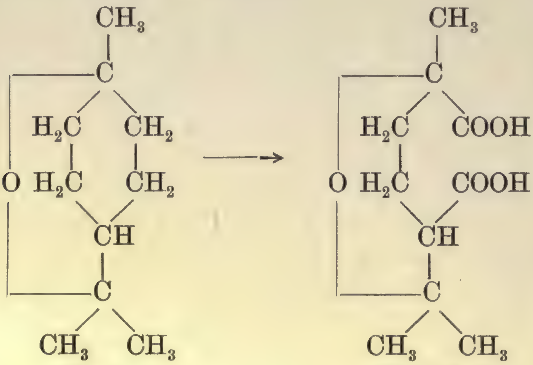
Cis-terpin. Cineol.

This formula is supported by the fact that hydrobromic acid in acetic acid solution converts cineol into cis-dipentene dibromide—



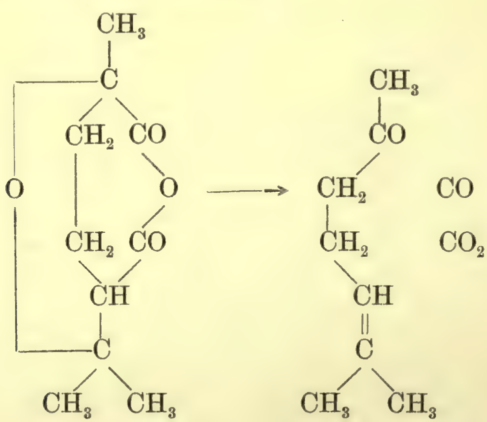
Cineol. Cis-terpin dibromide.

The behaviour of cineol on oxidation with potassium permanganate is curious.[1] The first effect is to break the hexamethylene ring, while leaving the ether chain untouched; in this way cineolic acid is produced—



Cineol. Cineolic acid.

When cineolic acid is treated with acetic anhydride it yields cineolic anhydride, which, on dry distillation, breaks down quantitatively into carbon monoxide, carbon dioxide, and methyl-heptenone, an aliphatic ketone of considerable interest from its relations to the terpenes—



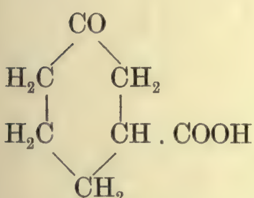
Cineolic anhydride. Methyl-heptenone.

[1] Wallach and Gildemeister, *Annalen*, 1888, **246**, 268; Wallach, *ibid.*, 1890, **258**, 319; Wallach and Elkeles, *ibid.*, 1892, **271**, 21.

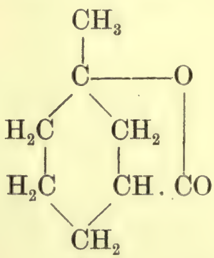
7. *The Synthesis of Carvestrene.*

Until quite recently, carvestrene could be obtained only by a very long and complicated series of reactions; and the constitutions of some of the intermediate compounds produced had not been well established. Perkin and Tattersall[1] have now succeeded in synthesizing it by a series of reactions analogous to those employed by Perkin in his synthesis of terpineol.

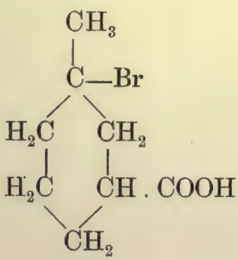
The starting-point of this new synthesis was *m*-hydroxybenzoic acid. This was first reduced with sodium and alcohol, forming hexahydro-*m*-hydroxy-benzoic acid; from which, by oxidation with chromic acid, γ-keto-hexahydrobenzoic acid (I.) was obtained. The ester of this acid reacts with magnesium methyl iodide, giving the lactone of γ-hydroxy-hexahydro-*m*-toluic acid (II.). When this is heated with hydrobromic acid it yields γ-bromohexahydro-*m*-toluic acid (III.), which on treatment with pyridine loses hydrobromic acid, and is changed into tetrahydro-*m*-toluic acid (IV.). After esterification, this is treated with magnesium methyl iodide and water, whereby an alcohol (V.) is produced which differs from terpineol in that the hydroxyl and methyl groups are in the 1, 3-position to each other, while in terpineol they are in the 1, 4-position. Just as terpineol, when treated with acid potassium sulphate, loses water to form dipentene, this new alcohol loses water and forms carvestrene (VI.)—



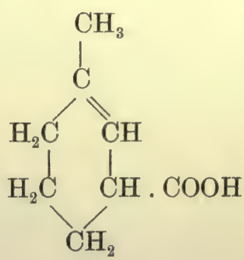
(I.)



(II.)

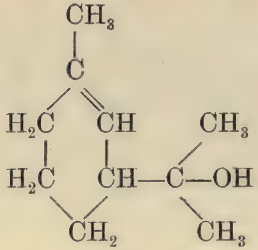


(III.)

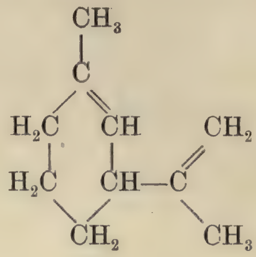


(IV.)

[1] Perkin and Tattersall, *Trans. Chem. Soc.*, 1907, **91**, 480.

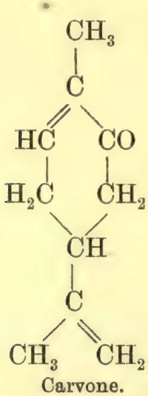


(V.)

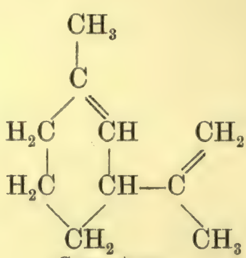


(VI.)

Though since the discovery of this new synthesis the old way of preparing carvestrene has lost its value as a practical method, we may give a very brief description of it here on account of one transition which occurs in the course of the reactions. The starting-point for the old synthesis was the substance carvone, which we have already encountered. Now, as can be seen from the formulæ of the two substances, to convert carvone into carvestrene we must shift the isopropylene group from one carbon atom to the adjacent one. How this is done will be seen in due course.



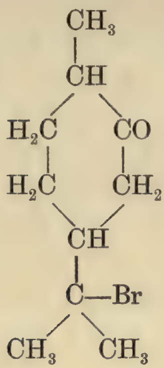
Carvone.



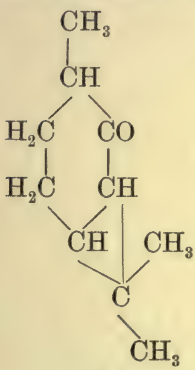
Carvestrene.

Carvone is first reduced with zinc dust and alcoholic potash to dihydrocarvone; hydrobromic acid is then added on, giving dihydrocarvone hydrobromide *—

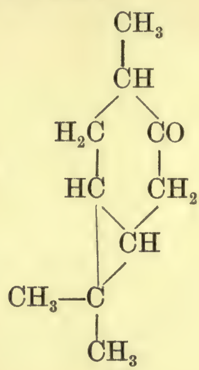
* When a halogen acid is added on to the double bond of an unsaturated substance, the negative part (*i.e.*, the halogen atom) always unites with that carbon atom to which the *fewest* hydrogen atoms are attached. For example, in



Now, when this substance is treated with alcoholic potash it gives up hydrobromic acid, but instead of regenerating a carvone derivative it yields a new ketone, carone. Since on oxidation carone yields 1, 1-dimethyl-2, 3-trimethylene dicarboxylic acid (caronic acid), it must contain a trimethylene ring. The simplest way in which this can be explained is to assume that carone has either of the formulæ (I.) and (II.).

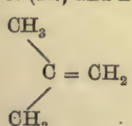


(I.)

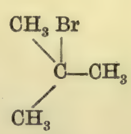


(II.)

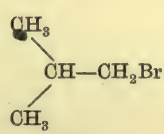
the case given below the compound formed by the addition of hydrobromic acid to (I.) is (II.) and not (III.).



(I.)



(II.)

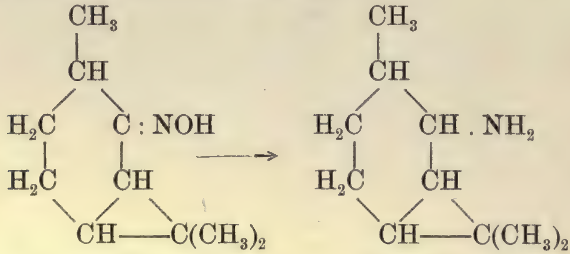


(III.)

This is called the "Markownikoff Rule" (*Ber.*, 1869, **2**, 660; *Annalen*, 1870, **153**, 256).

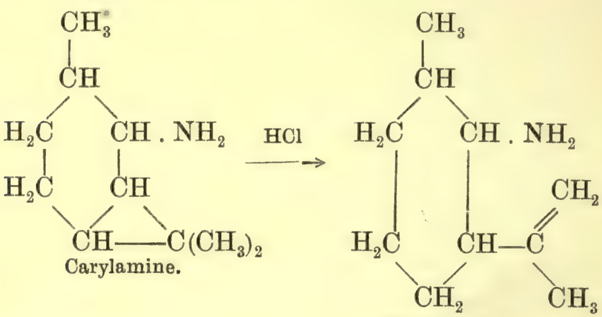
The first of these formulæ is the one usually ascribed to carone. We cannot enter into the details of the evidence here.

When carone is allowed to react with hydroxylamine it forms the substance carone oxime, which, on reduction, produces the amino-compound carylamine—



Carone oxime. Carylamine.

When this body is treated with alcoholic acid it undergoes isomeric change, and is converted into the hydrochloride of vestrylamine, the trimethylene ring being now broken. By this means we have transferred the isopropylene group from one carbon atom to the other—



Carylamine. Vestrylamine.

Vestrylamine hydrochloride, on dry distillation, breaks down into carvestrene by loss of ammonium chloride—

$$C_{10}H_{17}.NH_2.HCl = C_{10}H_{16} + NH_4Cl$$

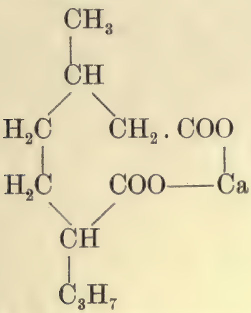
Carvestrene is a racemic compound, the dextro-antipode of which is found in nature as sylvestrene.[1] The latter has recently been synthesized by Perkin.[2]

[1] Baeyer, *Ber.*, 1894, **27**, 3485. [2] Perkin, *Proc.*, 1910, **26**, 97.

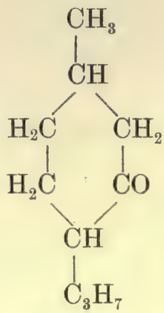
8. *The Synthesis of Menthone.*

Though menthone had been synthesized in different ways by Einhorn and Klages,[1] Kötz and Hesse[2] and Haller and Martine,[3] none of these methods furnished any proof of the constitution of the substance. It was not until 1907 that synthetic evidence was obtained upon this point.

Kötz and Schwarz[4] first synthesized β-methyl-α′-isopropyl-pimelic acid, and by the distillation of its calcium salt they produced menthone—

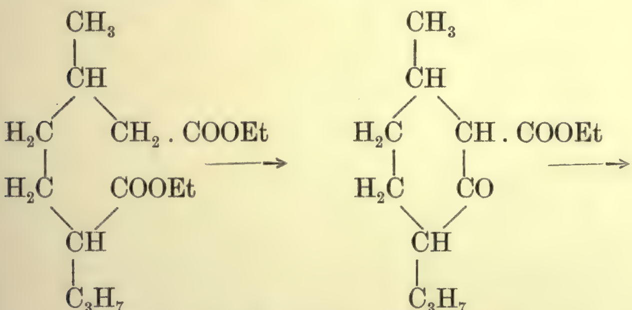


Calcium β-Methyl-α′-isopropyl-pimelate.

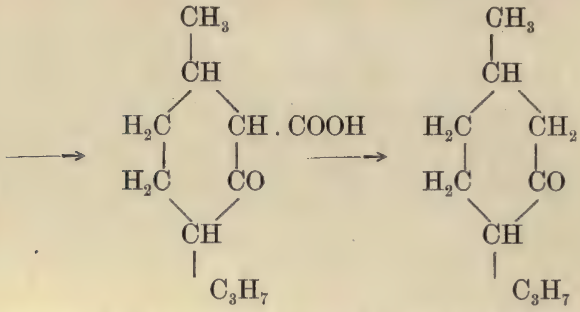


Menthone.

A similar result is obtained by making the ester of this acid undergo intramolecular acetoacetic ester condensation by means of sodium, and then hydrolyzing the ester thus obtained and splitting off carbon dioxide in the usual way—



[1] Einhorn and Klages, *Ber.*, 1901, **34**, 3793.
[2] Kötz and Hesse, *Annalen*, 1905, **342**, 306.
[3] Haller and Martine, *C. R.*, 1905, **140**, 130.
[4] Kötz and Schwarz, *Annalen*, 1907, **357**, 206.

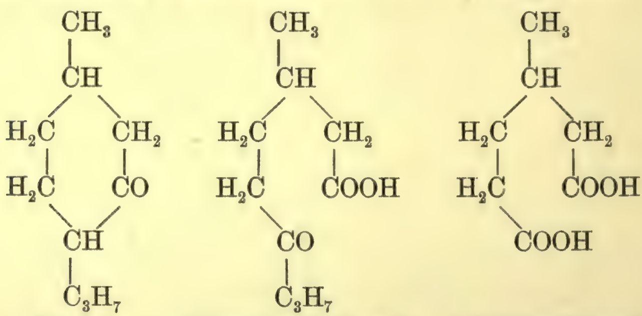


By means of this synthetic method, Kötz and Schwarz have produced an active menthone which is strongly dextro-rotatory.

9. *The Decompositions of Menthone.*

Before the discovery of the syntheses which we have just described, it had not been possible to show synthetically that the methyl and isopropyl radicles in menthone lay in the para-position to each other. The evidence for this had, however, been obtained from the decomposition reactions of menthone.

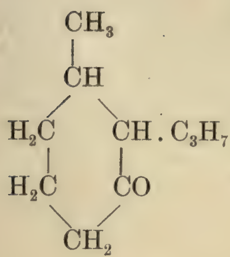
When menthone is oxidized by means of potassium permanganate, the first product is hydroxymenthylic acid,[1] which, on further oxidation, is converted into β-methyl-adipic acid—

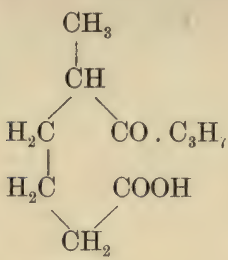


Menthone. Hydroxymenthylic acid. β-Methyl-adipic acid.

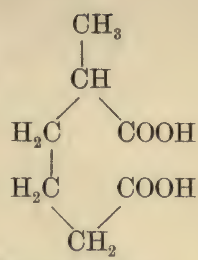
These substances could be formed only if the isopropyl and methyl radicles were in the para-position to each other; for if we take them in any other position, as shown below, the resulting products are not the same—

[1] Arth, *Ann. Chim. Phys.*, 1886, VI., 7, 433; Beckmann and Mehrländer, *Annalen*, 1896, **289**, 367.



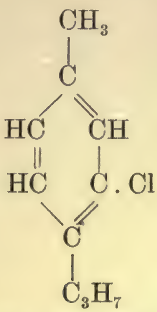


Keto-acid.



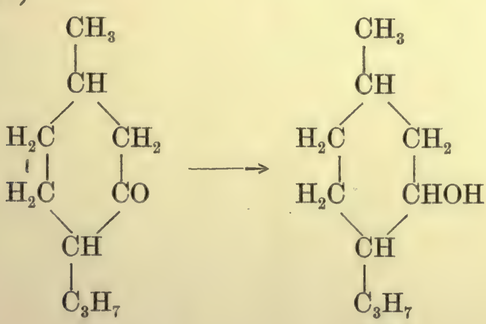
α-Methyl-adipic acid.

Again, the action of phosphorus pentachloride on menthone gives a dichloro-tetrahydro-cymene,[1] which, by successive treatment with bromine and quinoline, produces a chlorocymene[2] of the constitution—



10. *The Syntheses and Constitutions of Menthol and Menthene.*

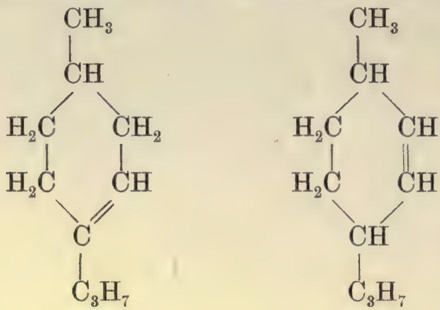
Menthol is the alcohol corresponding to menthone, from which it can be prepared by reduction. Since we have established that menthone is (I.) it is obvious that menthol must be (II.)—



(I.) (II.)

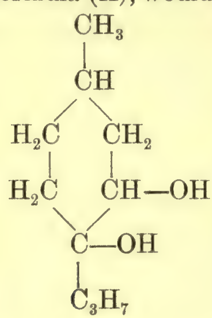
[1] Berkenheim, *Ber.*, 1892, **25**, 694.
[2] Jünger and Klages, *Ber.*, 1896, **29**, 314.

Now, when we dehydrate menthol, a hydrocarbon, *d*-menthene, is formed. This might be either (A) or (B), since we can suppose that water is removed in either of two ways—

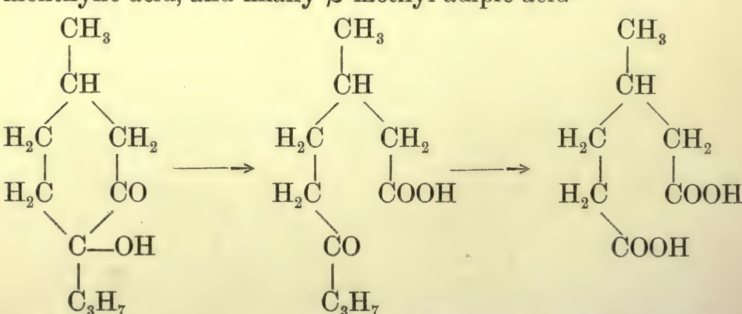


(A.) (B.)

The decision between the two formulæ can be made by the aid of the evidence of the oxidation products of menthene.[1] When the menthene obtained from menthol is oxidized with potassium permanganate solution, the first product is a glycol, which, according to formula (A), would have the constitution—



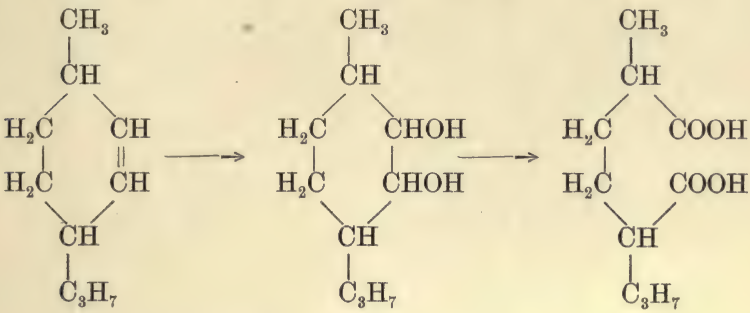
Further oxidation yields a ketone-alcohol, then hydroxymenthylic acid, and finally β-methyl-adipic acid—



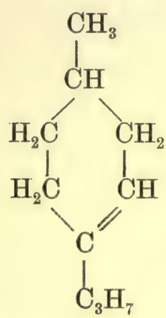
Ketone alcohol. Hydroxymenthylic acid. β-Methyl-adipic acid.

[1] Wagner, *Ber.*, 1894, **27**, 1639.

This is in agreement with the experimental results; but if, on the other hand, we start from the second possible formula for menthene, the oxidation products would not be those found in practice, but would be the compounds shown below—

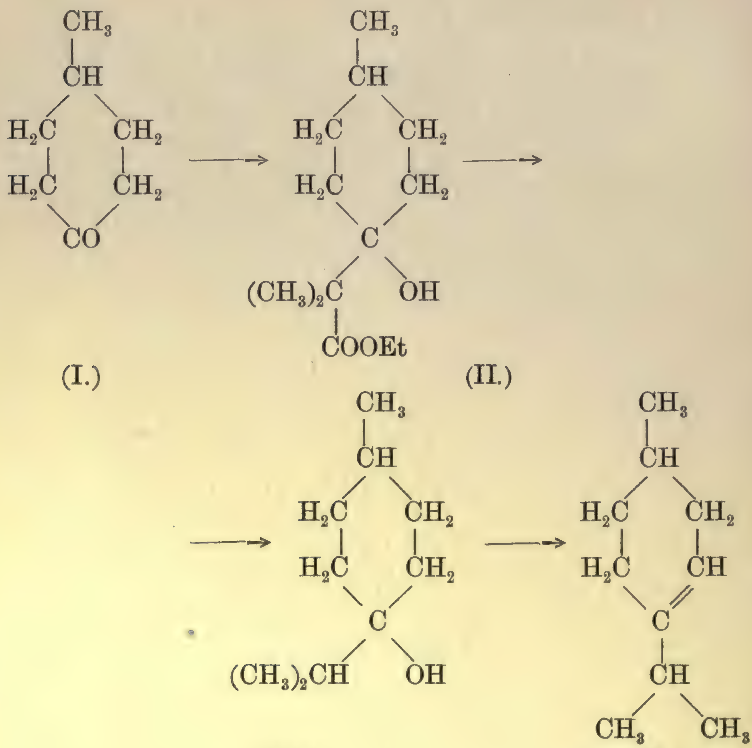


Thus the constitution of menthene must be—



This has been confirmed by Wallach's recent synthesis of menthene,[1] in which he chooses as his starting-point 1, 4-methyl-cyclohexanone (I.). This he condenses with *a*-bromo-isobutyric ester by means of zinc, forming (II.); and then, by hydrolysis and heating, causes the acid to lose carbon dioxide and become converted into an alcohol (III.), which, on boiling with sulphuric acid, loses water and yields menthene—

[1] Wallach, *Ber.*, 1906, **39**, 2504.

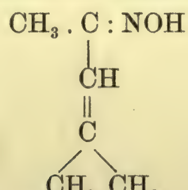


(I.) (II.) (III.) (IV.)
Menthene.

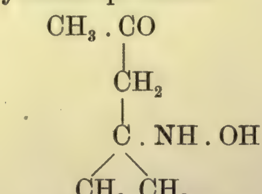
11. *The Constitution of Pulegone.*

The last compound of the menthone group with which we need deal is the unsaturated ketone pulegone.

If a ketone contains a double bond in the $\alpha\beta$-position to the carbonyl group, hydroxylamine may react with it in two ways, forming an oxime in the one case, and in the other attaching itself to the double bond to give a hydroxylamine derivative. For instance, in the case of mesityl oxide, we may have either mesityl oxime or diacetone-hydroxylamine produced—



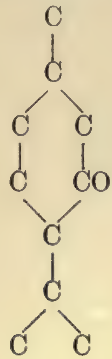
Mesityl oxime.



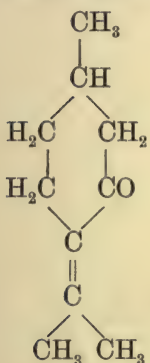
Diacetone-hydroxylamine.

Now, since pulegone shows a similar behaviour, forming either an oxime or a hydroxylamine derivative, the presumption is that it also is a ketone with an unsaturated group in the $\alpha\beta$-position to the carbonyl radicle.

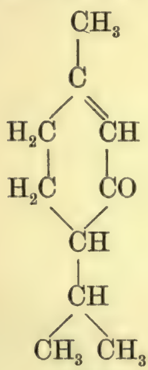
Again, pulegone on reduction is converted into menthone so that it must contain the skeleton—



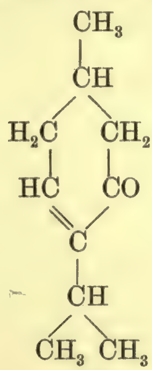
And since we have found that it has the properties of an $\alpha\beta$ unsaturated ketone it can have only three possible formulæ—



(A.)



(B.)

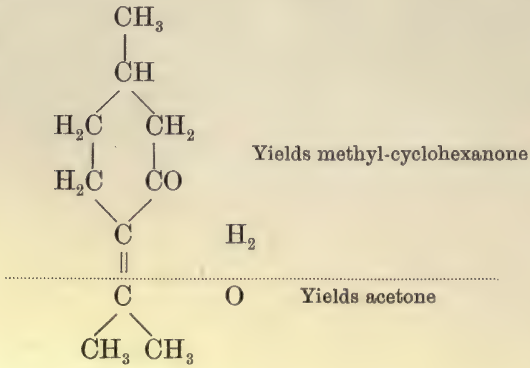


(C.)

The evidence which enables us to choose between these three has been supplied by Wallach,[1] who has shown that when pulegone is heated under pressure with water or anhydrous formic acid it undergoes decomposition into acetone and methyl-cyclohexanone. Since this reaction can be explained by Formula A alone, it is obvious that pulegone must have

[1] Wallach, *Annalen*, 1896, **289**, 337.

that constitution. The break-down may be formulated in the way indicated below—



CHAPTER III.

THE DICYCLIC TERPENES.

A.—The Camphene-Bornylene Group.

1. *Syntheses of Camphoric Acid.*

In the series of dicyclic terpenes which we are about to describe there are three important classes of substances. One group is derived from the hydrocarbon camphene, another from fenchene, and a third from pinene. Of these by far the most important is the camphene group, with which we shall deal first. The central substance of this group is the compound camphor, $C_{10}H_{16}O$; but in order to prove the constitution of this body it will be necessary to proceed step by step, and in the first place to prove the constitution of camphoric acid, which is obtained from camphor by oxidation.

Komppa[1] and, later, Perkin and Thorpe[2] have synthesized camphoric acid. We may deal with both of these syntheses, beginning with the method employed by Komppa.

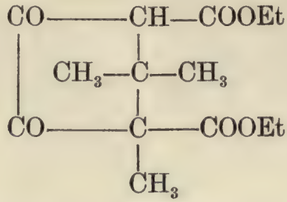
In this synthesis, the starting materials are oxalic ester and $\beta\beta$-dimethyl-glutaric ester. These are condensed together with sodium ethylate in the usual way, producing diketoapocamphoric ester—

$$
\begin{array}{l}
COOEt \quad H.CH.COOEt \\
| \qquad\qquad\quad | \\
| \qquad CH_3.C.CH_3 \\
| \qquad\qquad\quad | \\
COOEt \quad H.CH.COOEt
\end{array}
\xrightarrow{-2EtOH}
\begin{array}{l}
CO\text{———}CH\text{—}COOEt \\
| \qquad\qquad\quad | \\
| \quad CH_3\text{—}C\text{—}CH_3 \\
| \qquad\qquad\quad | \\
CO\text{———}CH\text{—}COOEt
\end{array}
$$

Diketoapocamphoric ester.

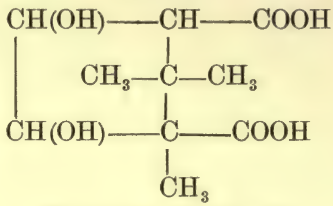
This was then methylated by means of sodium and methyl iodide, giving diketocamphoric ester—

[1] Komppa, *Ber.*, 1903, **36**, 4332; *Annalen*, 1909, **368**, 126; **370**, 209.
[2] Perkin and Thorpe, *Trans. Chem. Soc.*, 1906, **89**, 795.



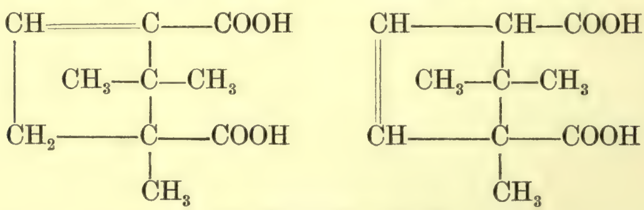
It is obvious that, since the formula is symmetrical, it makes no difference which hydrogen atom is replaced by the methyl group ; the end-product in each case is the same.

This diketo-ester was dissolved in sodium carbonate solution and then treated with sodium amalgam in a stream of carbon dioxide ; by this means the two carbonyl groups were reduced, and dihydroxycamphoric acid was formed, the ester being hydrolyzed by the alkaline solution—



Dihydroxycamphoric acid.

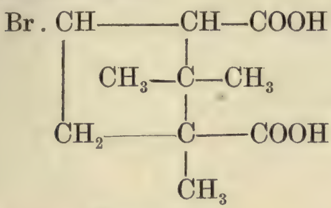
On boiling this substance with hydriodic acid in presence of red phosphorus, it is converted into dehydrocamphoric acid, which may have either of the constitutions shown below—



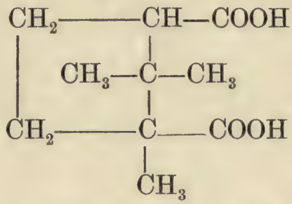
Dehydrocamphoric acid.

The constitution of this acid is of no importance, however, as the next two steps in the synthesis will yield the same final product from either of the two acids formulated above. The dehydrocamphoric acid is heated with hydrobromic acid in acetic acid solution to 125° C., whereby it is converted into a bromo-acid, which is then reduced with zinc dust and acetic

acid to a substance which is identical with ordinary racemic camphoric acid—



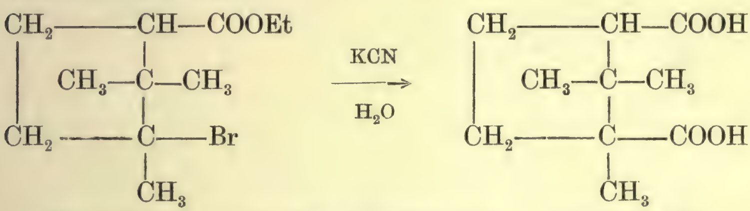
Bromo-acid.



Racemic camphoric acid.

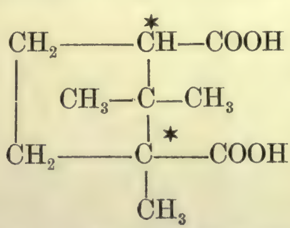
It will be seen at once that the exact constitution of the dehydrocamphoric acid is of no great importance, as the position of the bromine atom in the bromo-acid does not affect the constitution of the final camphoric acid.

The synthesis of Perkin and Thorpe starts from trimethyl-1, 2, 2-bromo-1-cyclopentane carboxylic ester, which is shaken with a mixture of potassium cyanide and hydrocyanic acid solutions. The resulting substance is heated and then boiled with acetic anhydride, whereby racemic camphoric anhydride is formed.



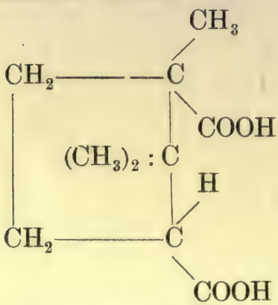
Trimethyl-bromo-cyclopentane carboxylic ester. Camphoric acid.

One peculiarity of camphoric acid may be pointed out here. An examination of the formula shows that camphoric acid has two asymmetric carbon atoms in its ring—these are distinguished by asterisks in the following formula :—

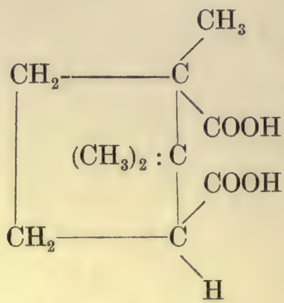


Now, when we attempt to racemize dextro-camphoric acid by any of the usual methods, it is found that instead of producing

an equimolecular mixture of dextro- and lævo-camphoric acids we obtain merely a mixture of dextro-camphoric acid with a new substance, lævo-*iso*-camphoric acid. From this behaviour of camphoric acid it is deduced that instead of both asymmetric carbon atoms in the dextro-acid being inverted (which would give us the mirror-image lævo-camphoric) only one is altered; so that half the molecule remains as it was. The change from *d*-camphoric to *l-iso*camphoric would be represented thus—



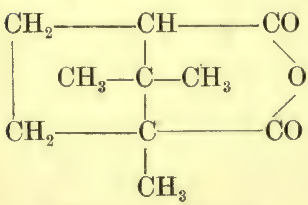
d-Camphoric acid.



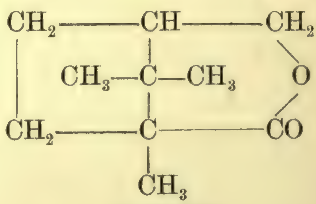
*l-Iso*camphoric acid.

2. *The Synthesis of Camphor.*

From synthetic camphoric acid we can obtain camphor itself by the following method. When camphoric anhydride is treated with sodium amalgam it is reduced to campholide,[1] the reaction being analogous to the production of phthalide from phthalic acid—



Camphoric anhydride.

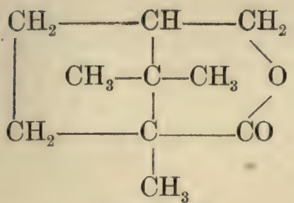


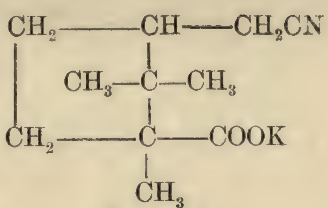
Campholide.

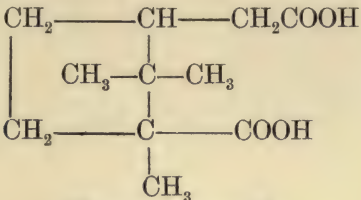
Campholide, on treatment with potassium cyanide, produces a nitrile-salt, which, on hydrolysis, gives homocamphoric acid;[2] this action is exactly like that which produces homophthalic acid from phthalide—

[1] Haller, *Bull. soc. chim.*, 1896, [iii.], **15**, 7, 984; Forster, *Trans. Chem. Soc.*, 1896, **69**, 36.

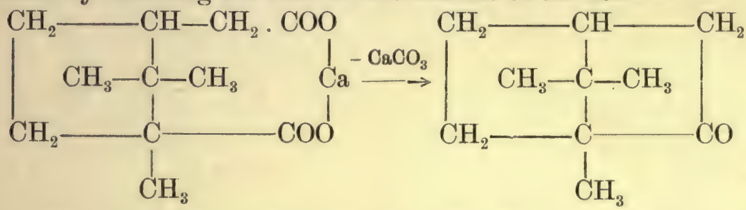
[2] Haller and Blanc, *C. R.*, 1900, **130**, 376.


Campholide.


Nitrile-salt.


Homocamphoric acid.

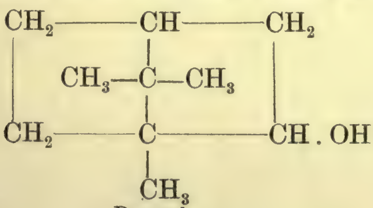
From this homocamphoric acid it is easy to produce camphor itself by distilling the lead or calcium salt of the acid—[1]



This synthesis confirms the camphor formula which was put forward in 1893 by Bredt.[2]

3. *Borneol and Camphane.*

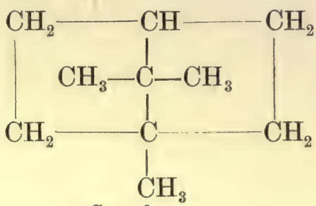
When camphor is reduced by means of sodium and alcohol[3] it yields a secondary alcohol, borneol, which has the formula—


Borneol.

[1] Haller, *C. R.*, 1896, **122**, 446; Bredt and Rosenberg, *Annalen*, 1896, **289**.
[2] Bredt, *Ber.*, 1893, **26**, 3047.
[3] Jackson and Mencke, *Am. Chem. J.*, 1883, **5**, 270; Wallach, *Annalen*, 1885, **230**, 225.

This alcohol occurs in dextro- and lævo-forms, either of which may be obtained at will by reducing the corresponding dextro- or lævo-camphor. Borneol is not the only product of this reaction, however, as at the same time a small quantity of an isomeric isoborneol[1] is produced, whose constitution is not yet definitely proved.

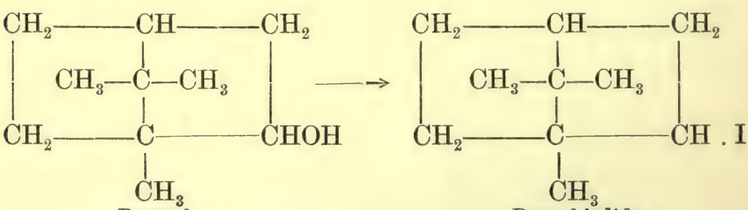
The hydroxyl radicle in borneol can be replaced by a halogen atom in the usual way,* and if the bornyl iodide thus formed be reduced by means of zinc dust, acetic and hydriodic acids,[2] a hydrocarbon camphane is produced, which is the root-substance of the camphor series. It has the formula—



Camphane.

4. *Bornylene.*

When bornyl iodide is heated with alcoholic potash to 170 it is converted into an unsaturated substance by the loss of a molecule of a halogen acid.[3] This compound, bornylene, on oxidation yields camphoric acid.



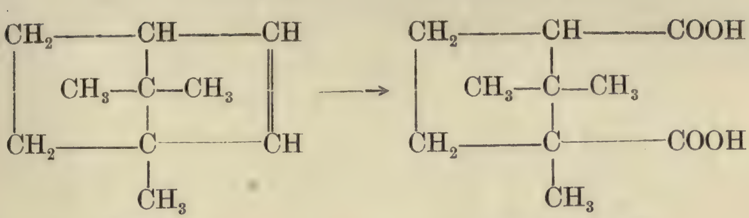
Borneol. Bornyl iodide.

[1] Montgolfier, *C. R.*, 1879, **89**, 101; Haller, *C. R.*, 1887, **105**, 227.

[2] Aschan, *Ber.*, 1900, **33**, 1006.

[3] Wagner and Brickner, *Ber.*, 1900, **33**, 2121.

* In practice, however, bornyl iodide is usually prepared by the action of hydriodic acid on pinene, as the yields from borneol are very poor.

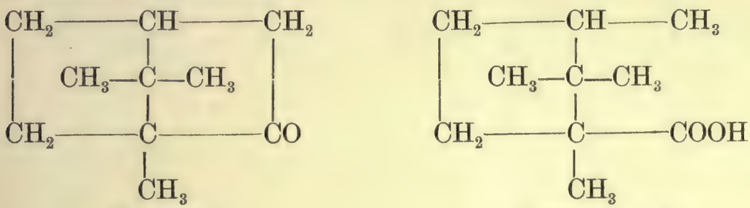


Bornylene. Camphoric acid.

Bornylene therefore has the structure shown above.

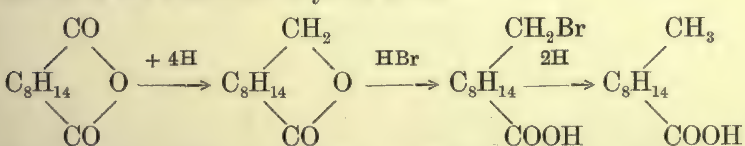
5. *The Decomposition Products of Camphor.*

Let us now return to the problem of camphor. The most vulnerable point in the camphor molecule is the carbonyl group and the adjacent methylene radicle. The ring at this point is so easily attacked that it may be broken by a simple hydrolytic reaction. When camphor is heated with sodium and xylene to a temperature of 280° C., the ring opens; and when the reaction mixture is poured into water, the sodium salt of campholic acid [1] is formed—



Camphor. Campholic acid.

The same acid has been obtained by Haller and Blanc [2] from campholide, a method of synthesis which establishes the constitution of the substance beyond doubt—

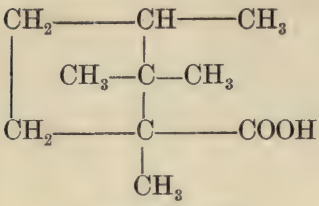


Camphoric anhydride. Campholide. Bromocampholic acid. Campholic acid.

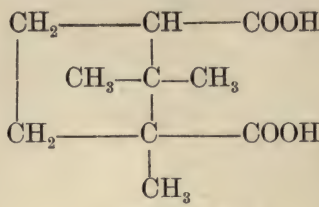
Now, when campholic acid is oxidized with nitric acid, the newly formed methyl group is oxidized to carboxyl, and camphoric acid is formed—

[1] Malin, *Annalen*, 1868, **145**, 201; Kachler, *ibid.*, 1872, **162**, 259.

[2] Haller and Blanc, *C. R.*, 1900, **130**, 376.

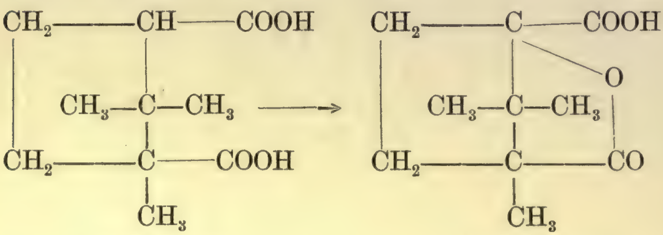


Campholic acid.

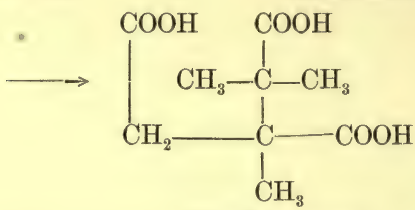


Camphoric acid.

Further action of nitric acid upon the latter substance gives rise to camphanic acid, which is oxidized in its turn to camphoronic acid—

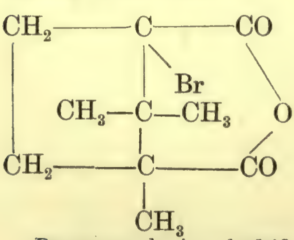


Camphoric acid. Camphanic acid.

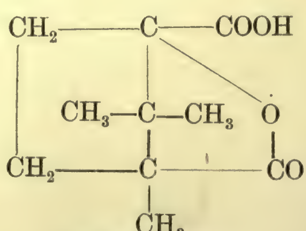


Camphoronic acid.

The constitution of camphanic acid[1] is proved by the fact that it can be obtained from bromocamphoric anhydride by boiling with water—



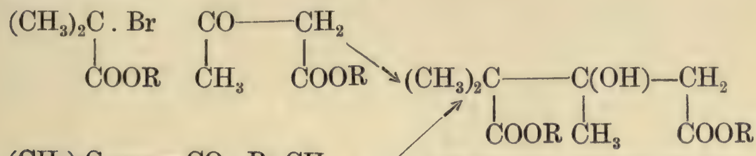
Bromocamphoric anhydride.



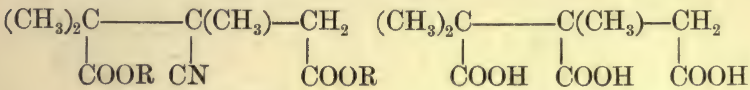
Camphanic acid.

[1] Reyher, "Dissertation," Leipzig, 1891; Bredt, *Ber.*, 1894, **21**, 2097; Lapworth and Lenton, *Trans. Chem. Soc.*, 1902, **81**, 17.

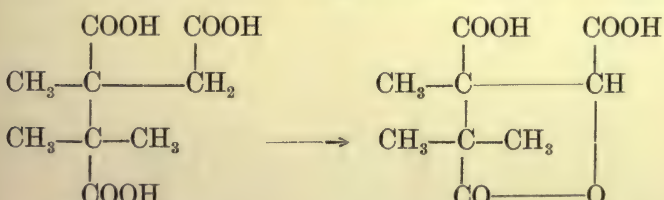
The constitution of camphoronic acid was established by the synthesis of Perkin and Thorpe.[1] These authors first prepared β-hydroxy-trimethyl-glutaric ester by the action of zinc upon a mixture of acetoacetic ester and α-bromo-isobutyric ester, or upon a mixture of dimethyl-acetoacetic ester and monobromacetic ester—


β-Hydroxytrimethylglutaric ester.

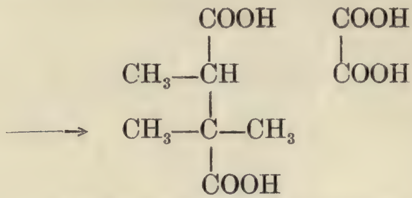
By replacing the hydroxyl group first with chlorine and then by cyanogen they obtained the nitrile ester of camphoronic acid, from which the acid itself was produced by hydrolysis—


Camphoronic nitrile. Camphoronic acid.

When camphoronic acid is heated to above 135° C., it loses water and is converted into anhydrocamphoronic acid, $C_9H_{12}O_5$. By brominating the chloride of this acid, two isomeric bromo-anhydrocamphoronic chlorides are produced, one of which, when boiled with water, gives the lactone of an unstable hydroxy-camphoronic acid (camphoranic acid), while the other yields stable hydroxycamphoronic acid. Camphoranic acid, when fused with potash, breaks down into oxalic and trimethyl-succinic acids.[2] These changes may be expressed thus—


Camphoronic acid. Camphoranic acid.

[1] Perkin and Thorpe, *Trans. Chem. Soc.*, 1897, **71**, 1169.
[2] Bredt, *Annalen*, 1898, **299**, 150.



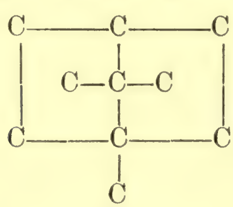
Trimethylsuccinic and oxalic acids.

6. *Camphene.*

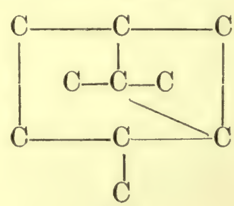
Camphene, $C_{10}H_{16}$, is a hydrocarbon isomeric with bornylene; but its constitution is still one of the enigmas of organic chemistry. It would occupy too much space were we to weigh the pros and cons of all the formulæ which have been proposed for the compound; and in the present section we can do little more than indicate the difficulties with which the problem is surrounded.[1]

In the first place, we may give two of the methods by which the hydrocarbon can be produced,* as these show how complex the question is, even in its earliest stages.

Berthelot[2] prepared it by heating pinene hydrochloride or hydrobromide with sodium stearate to 200°-220° C. Wallach[3] obtained it by dehydrating borneol with potassium bisulphate at 200° C. or by heating bornyl chloride with aniline. We already know that bornylene contains the skeleton (I.), and as we shall see later the pinene molecule contains the skeleton (II.),



(I.)



(II.)

so that even at this stage some intramolecular change must be

[1] For recent discussions of camphene's structure see Aschan, *Annalen*, 1910, **375**, 336; Lipp, *ibid.*, 1911, **382**, 265; Henderson and Heilbron, *Trans.*, 1911, **99**, 1901.

[2] Berthelot, *C. R.*, 1862, **55**, 496.

[3] Wallach, *Annalen*, 1885, **230**, 233, 239.

* Crude "camphene" appears to contain materials other than pure camphene (Aschan, *Annalen*, 1910, **375**, 336).

assumed during the formation of camphene from one or other of these groupings. Once the camphene skeleton is formed, it is extremely stable. Those reagents which usually produce intramolecular rearrangement act upon it only at high temperatures, and their effect is to bring about deep-seated changes in its structure.

When camphene is treated with bromine, the first reaction appears to be an addition of one molecule of the halogen; but this is immediately followed by a separation of hydrobromic acid, leaving a mono-bromocamphene.[1] By further action of bromine or by brominating camphene in ligroin solution at $-10°$ C., a halogen addition product, camphene dibromide,[2] is obtained which has the composition $C_{10}H_{16}Br_2$. A tribromide, $C_{10}H_{16}Br_3$, has also been obtained, which is probably formed partly by substitution and partly by addition.

Concentrated nitric acid forms with camphene an addition product containing equimolecular quantities of the two reagents.[3]

Hydrochloric acid acts upon camphene giving the chloride of an alcohol, isoborneol; whilst a mixture of sulphuric acid and acetic acid produces with camphene the acetate of the same alcohol.[4]

By the action of nascent nitrous acid upon camphene,[5] three compounds are simultaneously formed: camphene nitronitrosite, $C_{10}H_{16}(NO_2)_2 . NO$; camphene nitrosite, $C_{10}H_{16} . (NO_2) . NO$; and camphenylnitrite, $C_{10}H_{15} . O . N : O$. When the last compound is heated with potassium hydroxide solution it yields a ketone, camphenilone, $C_9H_{14}O$; whilst on reduction it produces camphenilan aldehyde, $C_9H_{15} . CHO$. The same aldehyde is formed from camphene by the action of chromyl chloride and hydrolysis with water.[6]

Oxidation of camphene with permanganate[7] produces camphene glycol, $C_{10}H_{16}(OH)_2$; whilst among the products of the reaction are two acids: camphene-camphoric acid,

[1] Wallach, *Annalen*, 1885, **230**, 233. [2] Reychler, *Ber.*, 1896, **29**, 900.

[3] Bouveault, *Bull. soc. chim.*, 1900, (3), **23**, 533.

[4] Bertram and Wahlbaum, *J. pr. Chem.*, 1894, (2), **49**, 8.

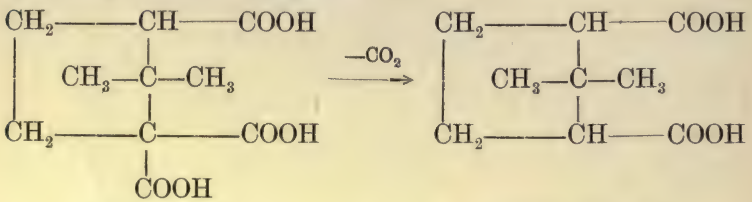
[5] Jagelki, *Ber.*, 1899, **32**, 1501.

[6] Bredt and Jagelki, *Annalen*, 1900, **310**, 112.

[7] Wagner, *Ber.*, 1890, **23**, 2311; *J. Russ. Phys. Chem. Soc.*, 1896, **28**, 64; 1897, **29**, 124; Wagner, Moycho and Zienkoffski, *Ber.*, 1904, **37**, 1032.

$C_8H_{14}(COOH)_2$, which is isomeric with camphoric acid; and camphenylic acid, $C_9H_{14}(OH) . COOH$.

When nitric acid[1] is substituted for permanganate, the first product isolated is camphoic acid, a tribasic acid which on heating loses carbon dioxide and produces apocamphoric acid. This reaction recalls the behaviour of malonic acid; and the constitution of camphoic acid is therefore assumed to be that which is shown below:—



Camphoic acid. Apocamphoric acid.

Camphoic acid is also obtained by the oxidation of dihydrocamphene.[2]

Henderson and Sutherland[3] obtained, among the oxidation products of camphene, iso-camphenilan aldehyde (supposed to be a stereoisomer of camphenilan aldehyde), camphenilone and an acid $C_{10}H_{16}O_2$, isomeric with iso-camphenilanic acid, into which it is transformed by heating with acetic anhydride.

When acted upon by chromic acid, camphene is converted into camphor.[4]

Finally, Henderson and Pollock[5] have shown that when camphene is reduced by Sabatier and Senderens' method it yields, not camphane, but an isomeric hydrocarbon.

We must now see how far this evidence takes us.

In the first place, it is clear that the syntheses of camphene throw no great light upon its constitution. Either the production of camphene from borneol or its formation from pinene hydrochloride must entail a molecular rearrangement, since these substances do not contain the same skeleton; and it is not impossible that both reactions are attended by intramolecular change.

[1] Marsh and Gardner, *Trans.*, 1891, **59**, 64; 1896, **69**, 74.

[2] Lipp, *Annalen*, 1911, **382**, 265.

[3] Henderson and Sutherland, *Trans.*, 1911, **99**, 1539.

[4] Armstrong and Tilden, *Ber.*, 1879, **12**, 1756.

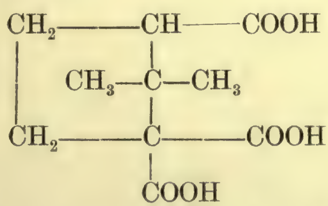
[5] Henderson and Pollock, *Trans.*, 1910, **97**, 1620; compare Lipp, *Annalen*, 1911, **382**, 265.

The reaction between camphene and bromine brings us a stage further. Ethylene derivatives sometimes react in this way, when at least one of the carbon atoms joined by the double bond carries a hydrogen atom. Further, the ready action of the halogen in the case of camphene leads to the conclusion that it probably contains some grouping such as $R_2:C:CH_2$ or $R_2:C:CHR$; since these are more readily attacked than the parent hydrocarbon. The possibility that the action of bromine is due to the presence of an easily-opened polymethylene ring in the camphene structure appears to be negatived by the reaction between the hydrocarbon and nitrous acid, which implies the presence of an ethylenic bond.

The behaviour of camphenyl nitrite with caustic potash points to its probably having the structure $C_9H_{14}:CH.O.N:O$; which would indicate that camphene itself contains the group $R_2C:CH_2$. A similar conclusion may be deduced from the formation of camphene glycol, which appears to be constituted [1] thus: $C_8H_{14}:C(OH).CH_2OH$; and also from the production of camphenilone, which is apparently a cyclic ketone formed by the rupture of the double bond between the methylene group and the rest of the molecule.

So far, all the evidence has pointed in one direction—to the probability that camphene contains a methylene radicle attached by a double bond to the rest of the molecule; and the fact that camphene, when reduced, yields something different from camphane supports this view strongly.

Now, however, we have to fit into this scheme the production of camphoic acid—



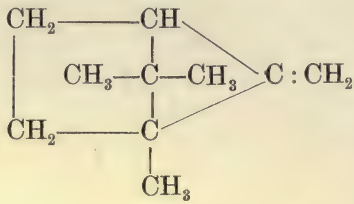
which is formed by the oxidation of either camphene itself or its reduction product.

It may be admitted frankly that, without assuming intramolecular change, the two sets of reactions cannot be forced

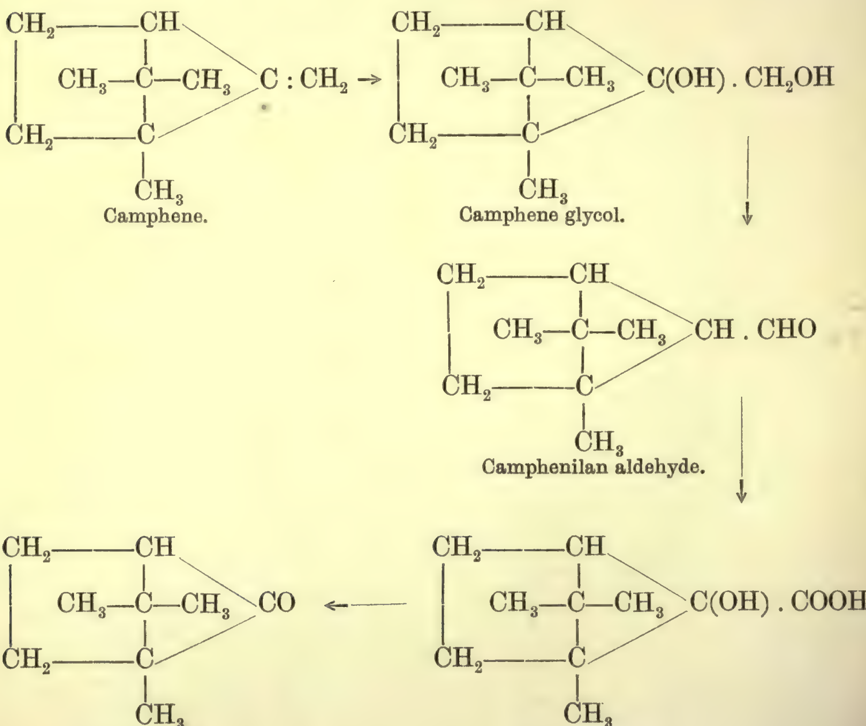
[1] Moycho and Zienkoffski, *Annalen*, 1905, **340**, 17.

into agreement. It cannot be denied that in camphoic acid all the carbon atoms of camphene are present; whereas by our previous assumptions one, at least, of them ought to have been lost during the oxidation with nitric acid.

The formula which appears to account best for the reactions of camphene was proposed by Semmler:—



According to this formula, the oxidation of camphene can be represented in the following manner:—

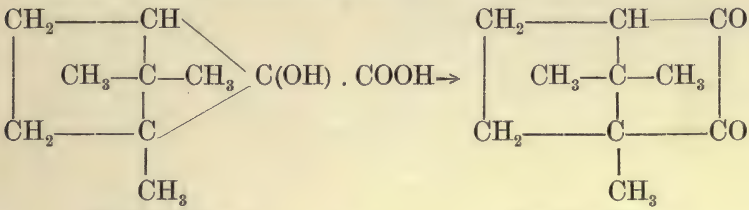


Camphene. Camphene glycol. Camphenilan aldehyde. Camphenylic acid. Camphenilone.

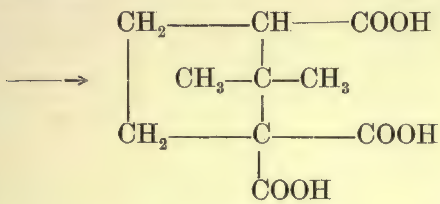
To account for the production of camphoic acid, it is necessary to assume the occurrence of a reaction inverse to the benzilic acid change, by means of which postulated reaction the group (I.) is converted into the group (II.)—

$$\text{(I.)}\quad \begin{matrix}R\\ R\end{matrix}\!\!>\!C(OH).COOH \longrightarrow \begin{matrix}R-CO\\ |\\ R-CO\end{matrix}\quad \text{(II.)}$$

On this basis, camphenylic acid would be produced as an intermediate product and converted into camphorquinone, which would at once be oxidized to camphoic acid—



Camphenylic acid. Camphorquinone.



Camphoic acid.

It cannot yet be asserted definitely that the camphene problem has been settled; so the above formulation must be received with caution.

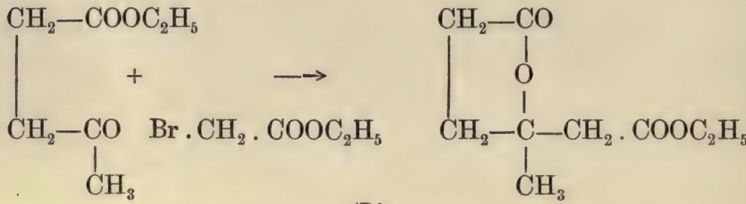
B.—Fenchene and its Derivatives.

1. *The Syntheses of Fenchone and Fenchyl Alcohol.*

Until quite recently, the exact constitution of fenchone had not been placed beyond doubt; for its degradation products are labile and difficult to utilize in the problem of determining the structure of the parent substance. A synthesis of the substance has now been attained, however, which establishes its constitution.[1]

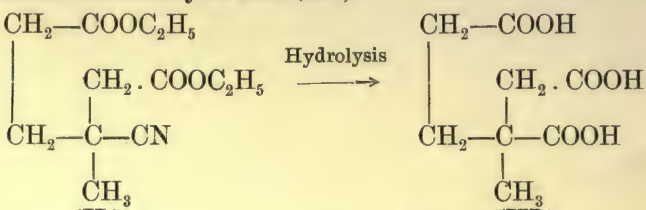
[1] Ruzička, *Ber.*, 1917, **50**, 1362.

The actual synthesis starts from lævulinic ester and bromacetic ester which are condensed together by means of zinc—



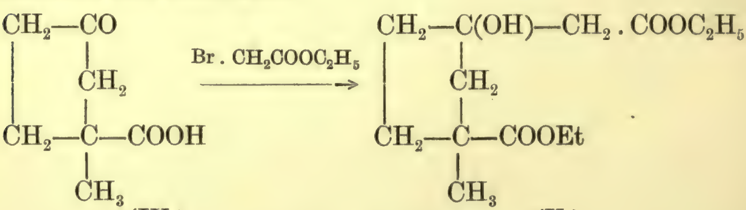
(I.)

The lactonic ester (I.) thus formed is heated with potassium cyanide, which converts it into the nitrile (II.). Hydrolysis yields the tricarboxylic acid (III.).



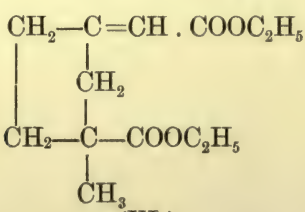
(II.) (III.)

On heating with sodium and benzene, this substance forms a pentamethylene derivative (IV.); and when the ethyl ester of this is condensed with *a*-bromoacetic ester in presence of zinc, a new chain is added, as shown in (V.). This compound apparently loses water and forms (VI.); for the reaction-mixture contains both materials—



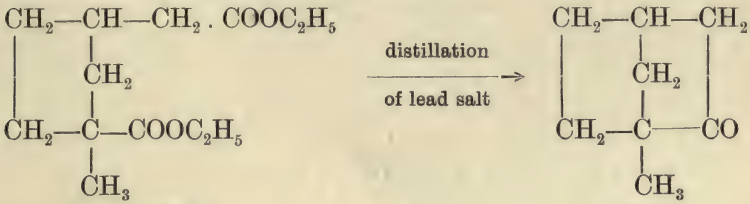
(IV.) (V.)

and



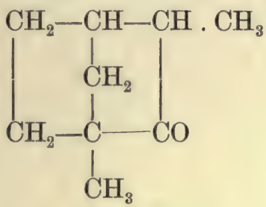
(VI.)

The mixture is treated with phosphorus tribromide in chloroform, which converts it all into (VI.); and then the ester is reduced to (VII.). The lead salt of this breaks down on distillation in the usual manner, forming the internal ketone, methyl*nor*camphor (VIII.).

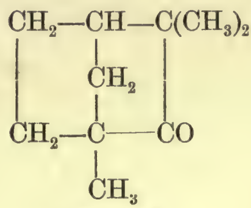


(VII.) (VIII.)

Methylation by means of sodamide and methyl iodide completes the process, producing a mixture of fenchosantenone (IX.) and racemic fenchone—



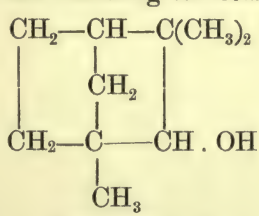
(IX.)



Fenchone.

This synthesis proves the correctness of the formula proposed for fenchone by Semmler.[1]

Reduction of fenchone produces fenchyl alcohol, which must therefore have the following structure :—



Fenchyl alcohol.

2. *The Decompositions of the Fenchenes.*

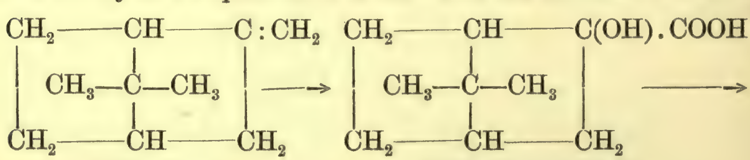
For a long time the structures of the fenchenes were a puzzle to organic chemists. As we have seen, the reduction

[1] Semmler, *Ch. Ztg.*, 1905, **29**, 1313; compare Bouveault and Levallois, *C. R.*, 1908, **146**, 180.

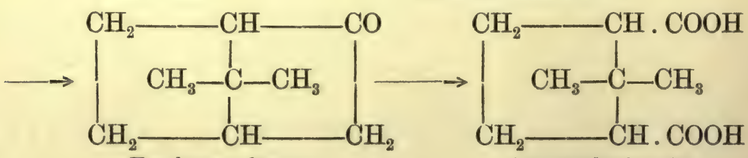
of fenchone yields fenchyl alcohol. It is found that *d*-fenchone gives rise to a lævo-rotatory alcohol, which is therefore described as D-*l*-fenchyl alcohol. When this is treated with phosphorus pentachloride at a low temperature it gives D-*l*-fenchyl chloride which, with aniline, loses hydrochloric acid and yields D-*l*-fenchene. This compound is now known as *α*-fenchene.[1]

If phosphorus pentachloride be allowed to act on fenchyl alcohol without cooling, a dextro-rotatory chloride is formed, which on treatment with aniline, produces D-*d*-fenchene, or *β*-fenchene. It is also possible to prepare *β*-fenchene by heating fenchyl alcohol with potassium hydrogen sulphate.[2]

The constitution of D-*l*-fenchene (*α*-fenchene) has been dealt with in the following way.[3] When it is oxidized with potassium permanganate it is converted into a hydroxy-acid, D-*l*-hydroxy-fenchenic acid, which has the composition $C_{10}H_{16}O_3$. This body, when treated with lead peroxide and sulphuric acid, loses carbon dioxide and two atoms of hydrogen, being converted into D-*d*-fenchocamphorone, $C_9H_{14}O$. By nitric acid this last compound is broken down to apocamphoric acid. This production of apocamphoric acid from fenchene shows that in fenchene itself one of the carbon atoms must be attached to the nucleus at a point different from that at which the methyl group in camphor is placed; as otherwise we should find camphoric acid produced in the end instead of its next lower homologue, apocamphoric acid. The only way in which we can satisfy this requirement is shown in the formulæ below—



D-*l*-fenchene. Hydroxyfenchenic acid.



Fenchocamphorone. Apocamphoric acid.

[1] Kommpa and Roschier, *Ann. Acad. Sci. fennicæ*, 1915, (A), 7, No. 14, 1.
[2] *Ibid.* [3] Wallach, *Annalen*, 1898, **300**, 294; 1901, **315**, 283.

D-*l*-fenchene, therefore, has the constitution expressed by—

$$\begin{array}{ccccc} CH_2 & — & CH & — & C:CH_2 \\ | & & | & & | \\ | & CH_3— & C & —CH_3 & | \\ | & & | & & | \\ CH_2 & — & CH & — & CH_2 \end{array}$$

How such a structure can arise by the dehydration of fenchyl alcohol or the removal of a molecule of hydrochloric acid from fenchyl chloride, is one of the puzzles of organic chemistry; and the matter is not made simpler by the occurrence of the second fenchene isomer.

With regard to the constitution of this β-fenchene, very little is known.[1] When prepared from racemic fenchyl alcohol and sodium hydrogen sulphate, it forms part of a mixture of hydrocarbons from which it can be separated by distillation. The pure product, on oxidation with alkaline permanganate, yields *r*-hydroxy-β-fenchenic acid, isomeric with hydroxy-fenchenic acid. Further oxidation, with acid permanganate, gives *r*-β-fenchocamphorone, isomeric with fenchocamphorone; and a final oxidation, this time with alkaline permanganate, produces a dibasic acid, $C_9H_{14}O_4$, an isomer of apocamphoric acid. This last compound gives no anhydride, which may point to it being a *trans*-compound. Beyond that, nothing is known of its structure.

C.—Pinene.

1. *The Constitution of Pinene.*

Pinene is a hydrocarbon isomeric with camphene and fenchene. It was found by Sobrero[2] that when this substance was allowed to stand in sunlight in contact with water and air it was, after several months, converted into a compound sobrerol,* $C_{10}H_{16}(OH)_2$, which, on boiling with dilute acids, was changed, by the loss of one molecule of water, into pinol, $C_{10}H_{16}O$. Pinol was found, on further investigation, to be an internal ether of the same type as cineol. Wallach[3] has shown

[1] Komppa and Roschier, *Ann. Acad. Sci. fennicæ*, 1915, (A), **7**, No. 14, 1.

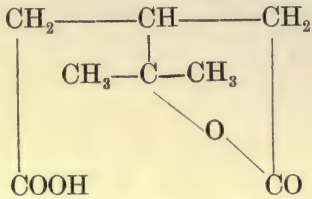
[2] Sobrero, *Annalen*, 1851, **80**, 106.

* Sobrerol can also be obtained by acting on pinene with mercuric acetate (Henderson and Agnew, *Trans.*, 1909, **95**, 289).

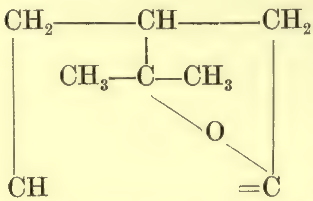
[3] Wallach, *Annalen*, 1890, **259**, 309.

that pinol may also be obtained by the action of sodium ethylate on terpineol dibromide.

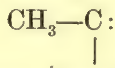
When pinol or sobrerol is treated with a 1 per cent. solution of potassium permanganate the product is a dihydric alcohol[1] pinol-glycol, $C_{10}H_{16}O(OH)_2$. On further oxidation, a tetrahydric alcohol[2] sobrerythrite, $C_{10}H_{16}(OH)_4$, is formed, which in turn is oxidized to terpenylic acid. Therefore we should find in pinene, pinol, and pinol-glycol, the same chain of carbon atoms which we know exists in terpenylic acid—



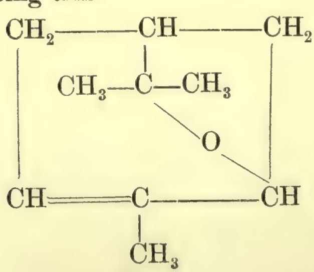
In other words, the pinol skeleton must contain the grouping—



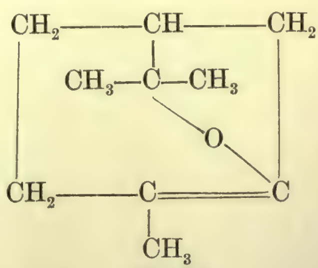
Into this scheme we have now to fit a hydrogen atom and the group—



and, as can at once be seen, there are two possible ways of doing this—



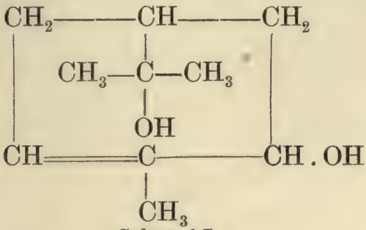
Pinol I.



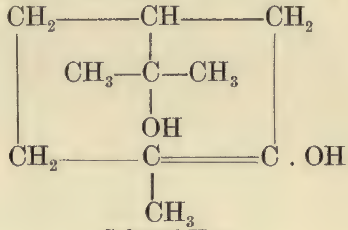
Pinol II.

[1] Wagner and Slawinski, *Ber.*, 1894, **27**, 1644.
[2] Wagner and Ginsberg, *Ber.*, 1894, **27**, 1648; 1896, **29**, 1195.

On these two assumptions sobrerol, which is obtained from pinol by the addition of water, would have either of the formulæ—

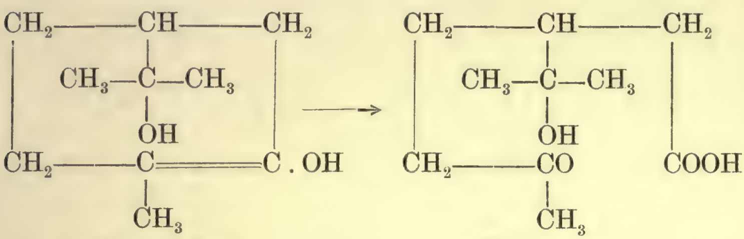


Sobrerol I.*a*.



Sobrerol II.*a*.

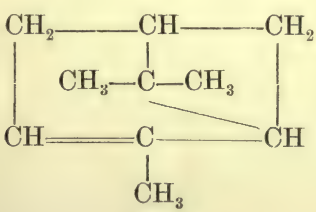
Now, sobrerol, on oxidation with a 1 per cent. solution of potassium permanganate, gives a tetrahydric alcohol, sobrerythrite. This can only be explained by using the formula (I.*a*), for (II.*a*) would produce a hydroxy-ketone—



Sobrerol II.*a*. Hydroxy-ketone.

Sobrerol, therefore, has the formula (I.*a*) and pinol the formula (I.).

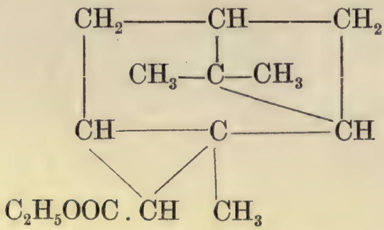
From this we may conclude that the formula of pinene itself is—



Pinene.

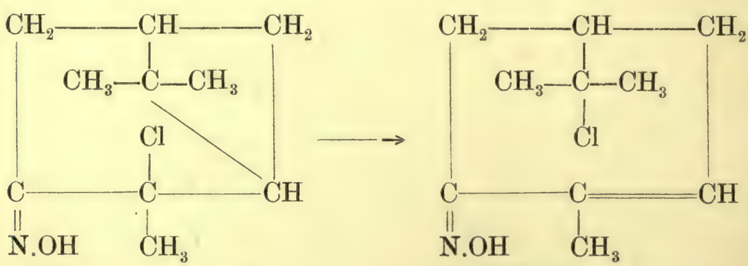
Further evidence in support of this constitution is supplied by the behaviour of pinene with diazo-acetic ester. It is well known that the latter body interacts with compounds

containing ethylenic bonds to produce pyrazolin derivatives, which then decompose, yielding trimethylene compounds.[1] Now when pinene and diazo-acetic ester interact, the end-product is a substance of the following structure :—[2]



and since we know that the ring is formed partly from the two atoms between which the double bond originally existed, this tends to establish the pinene formula which was deduced above.

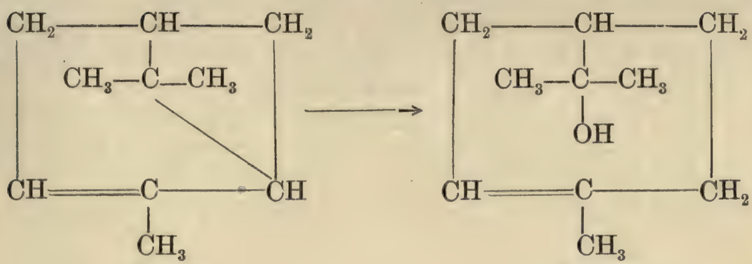
In virtue of the double bond in its molecule, pinene is capable of uniting with hydrochloric acid or nitrosyl chloride. Pinene hydrochloride resembles camphor in appearance and smell, and is used commercially under the name of "artificial camphor". Pinene nitrosochloride,[3] on standing in presence of hydrochloric acid, is converted into hydrochlorocarvoxime by the wandering of a chlorine atom and the rupture of the pinene tetramethylene ring—



Pinene nitrosochloride. Hydrochlorocarvoxime.

Pinene itself is converted into terpineol by hydration with dilute acids—

[1] Buchner and Curtius, *Ber.*, 1885, **18**, 237.
[2] Buchner and Rehorst, *Ber.*, 1913, **46**, 2680, 2687.
[3] Baeyer, *Ber.*, 1896, **29**, 20.



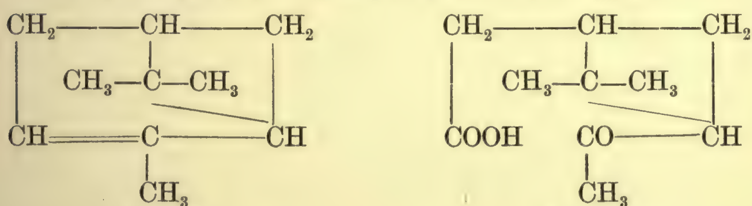
Pinene. Terpineol.

2. *Pinonic and Pinic Acids.*

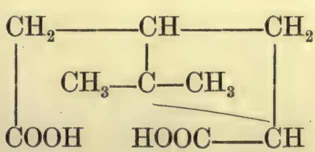
When pinene is oxidized with potassium permanganate, the first product is a ketonic acid[1] which, according to the conditions of the experiment, can be obtained either as a single substance or as a mixture of two isomers. When the single substance is produced it is found to have the composition $C_{10}H_{16}O_3$, and has been named *a*-pinonic acid. It contains the group CH_3-CO-, for, on treatment with bromine and potash, it loses a methyl group, takes up hydroxyl, and is converted into pinic acid, $C_9H_{14}O_4$—

$$\underset{\text{Pinonic acid.}}{C_8H_{13}O_2\text{—CO—}CH_3} \xrightarrow{\text{KOH and Br}} \underset{\text{Pinic acid.}}{C_8H_{13}O_2\text{—COOH}} + CHBr_3$$

These changes are expressed in the following formulæ :—



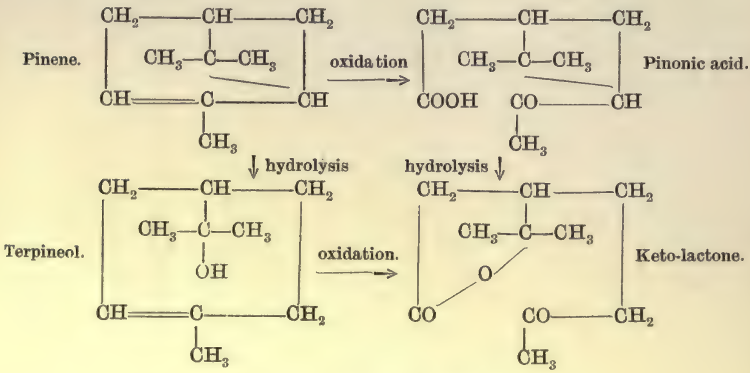
Pinene. Pinonic acid.



Pinic acid.

[1] Baeyer, *Ber.*, 1896, **29**, 3.

Now, on hydrolysis with 50 per cent. sulphuric acid, pinonic acid gives a keto-lactone,[1] $C_{10}H_{16}O_2$, which proves to be identical with that obtained in the oxidation of terpineol. A similar hydrolysis converts pinene into terpineol, so that the following scheme shows the relations between the four substances :—



[1] Baeyer, *Ber.*, 1896, **29**, 3.

CHAPTER IV.

THE OLEFINIC TERPENES.

A.—Introduction.

We have now described the most important cyclic terpenes, and in pursuance of the plan laid down in the first section dealing with these bodies, we must next examine the olefinic substances which are often included in the terpene group. It might have been more logical to have dealt with the open-chain compounds first, and the cyclic ones later, but as we should in that case have had to assume the constitution of certain cyclic terpenes which are closely connected with the olefinic ones, the present method of arrangement is more convenient.

Those unsaturated open-chain substances which are found in ethereal oils, and which, in many cases, can be transformed into cyclic terpenes, are termed olefinic terpenes, or terpenogens. They occur as hydrocarbons, aldehydes, or alcohols, and are derived from hydrocarbons of the formula C_5H_8. In many cases the odour of ethereal oils is very largely due to the olefinic terpenes contained in them.

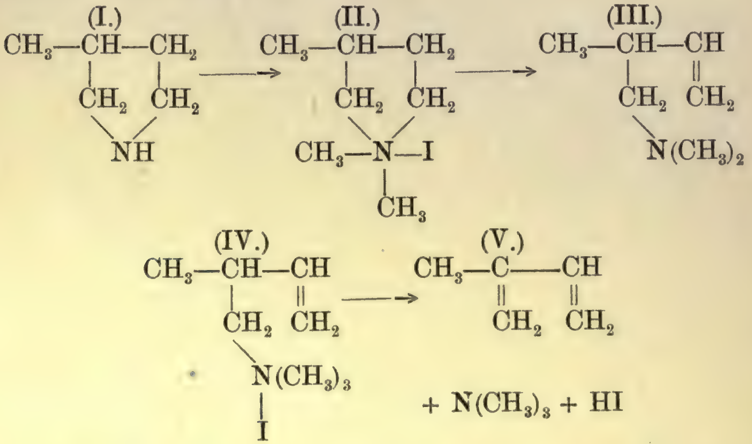
The chemical importance of the olefinic terpenes lies in the fact that from them we can build up some of the more complicated terpene derivatives by means of very simple reactions; but they are of interest also from the commercial point of view as forming the basis of many natural and artificial perfumes.

B.—Isoprene.

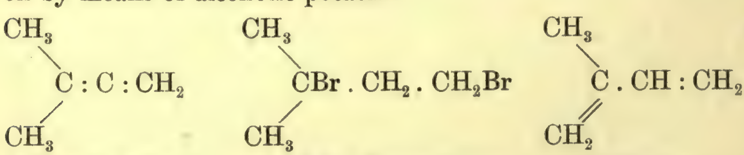
Isoprene is the simplest of all the olefinic terpenes; it contains two double bonds, and has the composition C_5H_8. Its synthesis has been carried out by Euler,[1] and also by Ipatjew,[2] in the one case starting from methyl-pyrrolidine, and in the

[1] Euler, *J. pr. Ch.*, II., **57**, 132. [2] Ipatjew, *ibid.*, **55**, 4.

other from dimethyl-allene. In the first case, the methyl-pyrrolidine (I.) is allowed to interact with methyl iodide with the formation of dimethyl-methylpyrrolidinium iodide (II.). This substance is then decomposed with potash, whereby the ring is broken and *des*-dimethyl-methylpyrrolidine (III.) is produced. The addition of methyl iodide and decomposition of the product (IV.) with potash gives trimethylamine and the required isoprene (V.)—



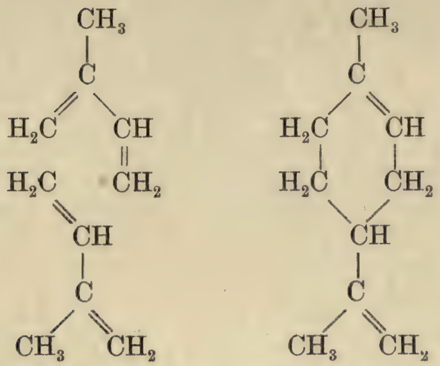
The synthesis from dimethyl-allene is much simpler. Two molecules of hydrobromic acid are added on, forming 2-methyl-2, 4-dibromobutane, from which hydrobromic acid is again split off by means of alcoholic potash—



Dimethyl-allene. Methyl-dibromobutane. Isoprene.

Isoprene is produced by the dry distillation of indiarubber and by the decomposition of turpentine oil at a dull red heat. Concentrated hydrochloric acid converts it into a polymer which has all the physical properties of indiarubber, and the same change takes place on long standing or with traces of acids in sunlight. When heated to 300° C., isoprene is polymerized to a di-isoprene,[1] which seems to be identical with dipentene—

[1] Tilden, *Trans. Chem. Soc.*, 1884, **45**, 410; Bouchardat, *C. R.*, 1875, **80**, 1446; 1878, **87**, 654; 1879, **89**, 361, 1117.



In a somewhat similar manner isoprene might be supposed to give a sesquiterpene in which three isoprene molecules would coalesce to form a compound of the composition $C_{15}H_{24}$. In any probable reaction of this type, it is worth noting, at least one unsaturated chain will be left untouched and ready to react with further molecules if the proper conditions are obtained; and it is doubtless to this side chain that we owe the more complex polymer which resembles indiarubber.

C.—Citronellal.

We must now pass to the consideration of a substance rather more complicated than isoprene—the compound citronellal, which was discovered by Dodge[1] in citronella oil. Citronellal is an aldehyde, for on reduction it gives the alcohol citronellol, and on oxidation it forms citronellic acid. Since it is optically active it must contain an asymmetric carbon atom.

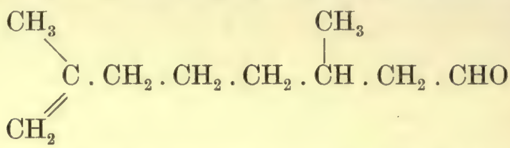
Tiemann and Schmidt,[3] oxidizing it in *aqueous* solution, obtained as products acetone and β-methyl-adipic acid, from which they concluded very naturally that citronellal had the constitution—

$$(CH_3)_2C=CH\,.\,CH_2\,.\,CH_2\,.\,CH(CH_3)\,.\,CH_2\,.\,CHO$$
$$\downarrow$$
$$(CH_3)_2CO + \underset{\displaystyle COOH}{\underset{|}{CH_2}}\,.\,CH_2\,.\,CH(CH_3)\,.\,CH_2\,.\,COOH$$

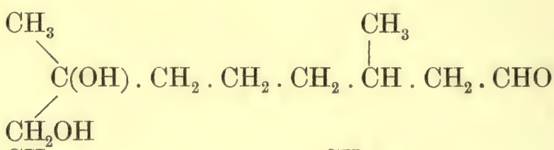
[1] Dodge, *Am. Chem. J.*, 1889, **11**, 456.
[2] Tiemann and Schmidt, *Ber.*, 1896, **29**, 903; 1897, **30**, 22, 33.

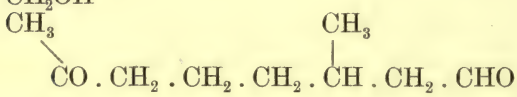
The reason for placing the methyl group in this position will be seen later when we deal with the production of pulegone from this body.

This constitution, however, is not in agreement with the work of Harries and Schauwecker,[1] who approached the matter from a slightly different standpoint. Instead of oxidizing citronellal itself, they prepared its dimethyl-acetal and replaced the aqueous solution of Schmidt and Tiemann by an acetone one. Under these circumstances they found that the oxidation product with potassium permanganate was the acetal of a dihydroxy-dihydrocitronellal, which, on further oxidation with chromic acid, could be converted into a keto-aldehyde. This shows that the double bond must lie at the extreme end of the chain, so that citronellal would have the constitution—



On this view the dihydroxy-compound and the keto-aldehyde would be—



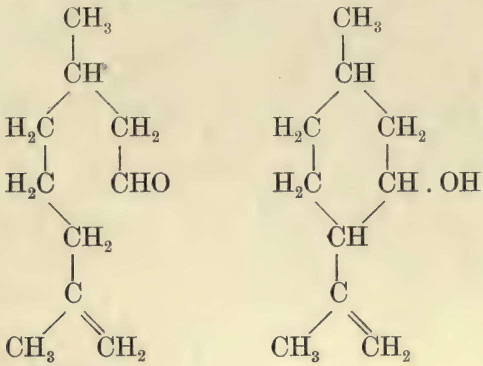


The results obtained by Tiemann and Schmidt would be explained by supposing that under the influence of the aqueous oxidizing agent the position of the double bond was changed from the ultimate to the penultimate pair of carbon atoms in the chain.

So far we have not proved the position of the methyl group, but we shall now give some evidence bearing upon the point. When citronellal is allowed to stand by itself for a considerable time it is converted into the isomeric substance isopulegol.[2]

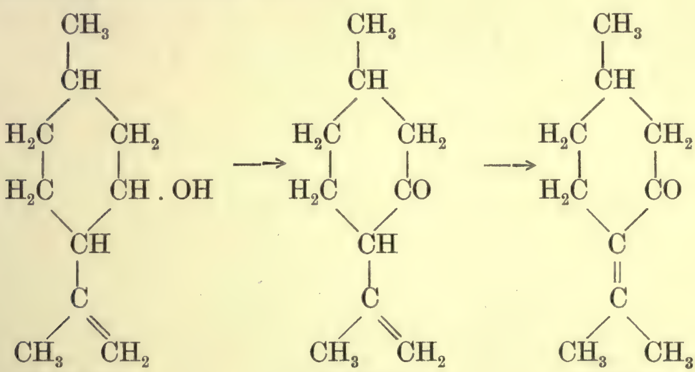
[1] Harries and Schauwecker, *Ber.*, 1901, **34**, 1498, 2981.
[2] Labbe, *Bull. soc. chim.*, 1899, [iii.], **21**, 1023.

The same change is brought about more rapidly by heating citronellal with acetic anhydride [1] to 180° C. The change may be represented in the following manner:—



Citronellal. Isopulegol.

The proof of the constitution of isopulegol depends upon its conversion into pulegone. When it is oxidized it yields the ketone isopulegone, which is converted into pulegone by the wandering of a double bond—



Isopulegol. Isopulegone. Pulegone.

From this it is evident that the methyl group in citronellal must be in the position which we attributed to it; as otherwise the isopropylene group would not come into the 1, 4-position with it in the pulegone formed from citronellal.

We may postpone the consideration of the alcohol citronellol and of citronellic acid until later, as they are closely connected

[1] Tiemann and Schmidt, *Ber.*, 1896, **29**, 913; **30**, 27.

with some members of the class of compounds with which we are about to deal in the next section.

D.—The Citral Group.

1. *General.*

The group of olefinic terpenes, of which citral is the most important member, can all be derived from the unsaturated ketone methyl-heptenone. It will perhaps be best, before entering upon a detailed consideration of the group, to give a small table showing the relations between the different members:—

$$
\begin{tikzcd}[column sep=tiny]
 & & & \text{Methyl-heptenone} \arrow[d] & & & \\
 & & & \text{Geranic acid} \arrow[dll] \arrow[drr] & & & \\
 & \text{Citral} \arrow[dl] \arrow[dr] & & & & \text{Rhodinic acid} \arrow[dl] \arrow[dr] & \\
\text{Geraniol} \arrow[d] & & \text{Nerol} & & \text{Rhodinol} & & \text{Rhodinal} \\
\text{Linalool} & & & & & &
\end{tikzcd}
$$

We must now proceed to trace out the various changes by which the several substances are obtained.

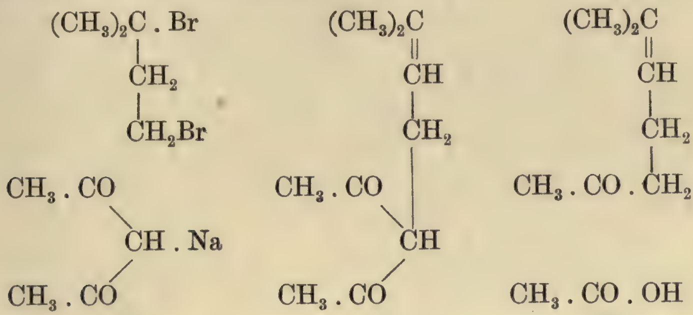
2. *Methyl-heptenone.*

As can be seen from the foregoing table, the substance from which all the other members of the citral group are built up is the ketone methyl-heptenone. We have already encountered this compound among the decomposition products of cineolic acid, but in that place we did not deal with its constitution.

Methyl-heptenone has been synthesized in different ways by Barbier and Bouveault,[1] Verley,[2] Tiemann,[3] Leser,[4] and Ipatjew.[5] We need only give one synthesis here, and may choose that of Barbier and Bouveault. In the first place, 2-methyl-2, 4-dibromobutane is condensed with the sodium derivative of acetylacetone. This gives the unsaturated dike-

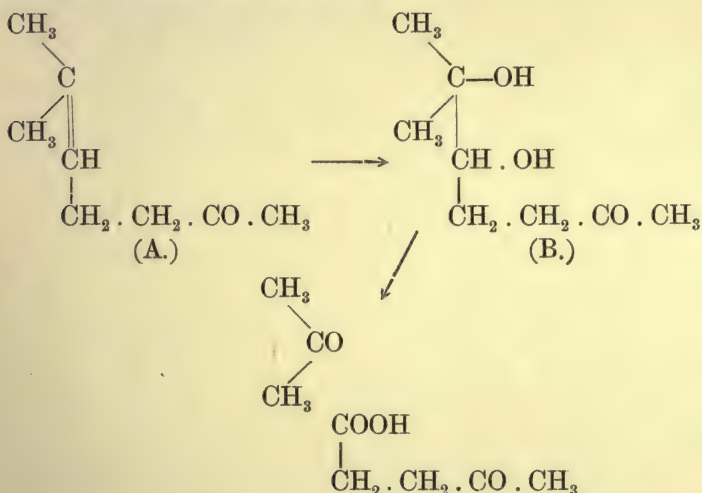
[1] Barbier and Bouveault, *C. R.*, 1896, **122**, 393.
[2] Verley, *Bull. soc. chim.*, 1897, [iii.], **17**, 180.
[3] Tiemann, *Ber.*, 1898, **31**, 824.
[4] Leser, *Bull. soc. chim.*, 1897, [iii.], **17**, 180.
[5] patjew, *Ber.*, 1901, **34**, 594.

tone (II.), which can be broken down by strong alkali into acetic acid and methyl-heptenone (III.)—



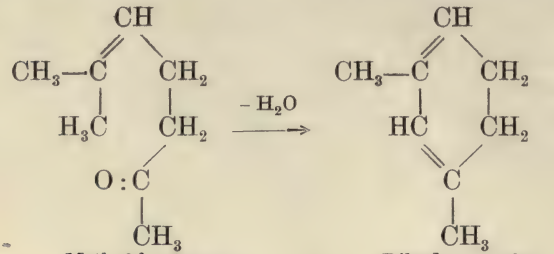
(I.) (II.) (III.)

This establishes the constitution of the substance, but if further proof were required it is to be found in the behaviour of methyl-heptenone (A) on oxidation. The first product (B) is a dihydroxy-ketone, which, on further oxidation, breaks down into acetone and lævulinic acid (C)—



(A.) (B.) (C.)

In itself, methyl-heptenone is of no great importance, and we may confine ourselves to one of the reactions which it undergoes. When shaken with 75 per cent. sulphuric acid it loses a molecule of water and is converted into dihydro-*m*-xylene—



Methyl-heptenone. Dihydro-*m*-xylene.

3. *Geranic Acid.*

Following upon their synthesis of methyl-heptenone, Barbier and Bouveault[1] were enabled to synthesize geranic acid by means of a simple series of reactions. By the action of zinc and iodo-acetic ester upon methyl-heptenone they prepared a hydroxy-acid, which, on boiling with acetic anhydride, broke down into geranic acid.

The formulæ below indicate the course of the synthesis—

$$(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2\,.\,\overset{\overset{\displaystyle CH_3}{|}}{C}O \qquad \text{Methyl-heptenone.}$$

$\downarrow$ *Zinc and iodoacetic ester*

$$(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2\,.\,\underset{\underset{\displaystyle CH_2\,.\,COOEt}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}\,.\,OZnI \qquad \text{Intermediate product.}$$

$\downarrow$ *Water*

$$(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2\,.\,\underset{\underset{\displaystyle CH_2\,.\,COOEt}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}\,.\,OH \qquad \text{Hydroxydihydrogeranic ester.}$$

$\downarrow$ *Hydrolysis*

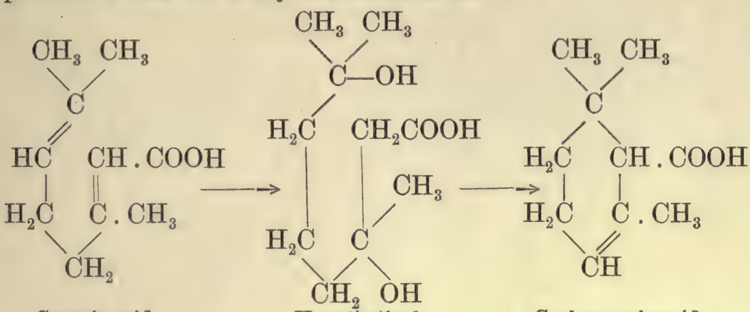
$$(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2\,.\,\underset{\underset{\displaystyle CH_2COOH}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}\,.\,OH \qquad \text{Hydroxydihydrogeranic acid.}$$

$\downarrow$ *Dehydration with acetic anhydride*

$$(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2\,.\,\overset{\overset{\displaystyle CH_3}{|}}{C}:CH\,.\,COOH \qquad \text{Geranic acid.}$$

[1] Barbier and Bouveault, *C. R.*, 1896, **122**, 393; see also Tiemann, *Ber.*, 1898, **31**, 825.

Like methyl-heptenone, geranic acid is of very little importance in itself. The only reaction which specially concerns us is its condensation to α-cyclogeranic acid,[1] which, like the corresponding condensation of methyl-heptenone, takes place under the influence of 70 per cent. sulphuric acid. In order to explain the geranic acid change, it is necessary to assume the formation and decomposition of an intermediate product which has not yet been isolated—



Geranic acid. Hypothetical intermediate product. α-Cyclogeranic acid.

As the table shows, geranic acid gives rise to two series of compounds: on the one hand, by reduction, we may obtain rhodinic acid and its derivatives; while on the other we may produce the aldehyde citral, from which in turn several substances may be formed. In the first place, we may deal with the smaller group, rhodinic acid and its allied compounds.

4. *Rhodinic Acid, Rhodinol, and Rhodinal.*

When the ethyl ester of geranic acid is reduced by means of sodium and amyl alcohol it is converted into inactive rhodinic acid.[2] The active, lævo-rotatory form of this acid has been obtained from the active alcohol rhodinol. These two acids are isomeric with citronellic acid, which is obtained by the oxidation of the aldehyde citronellal, and it has been suggested that citronellic acid is the dextro-form of rhodinic acid. On the other hand, from the constitution of citronellal, we should expect that citronellic acid obtained from it by oxidation would have the formula (I.), while rhodinic acid from geranic acid should have the formula (II.).

[1] Tiemann and Semmler, *Ber.*, 1893, **26**, 2726; Tiemann and Schmidt, *ibid.*, 1898, **31**, 881; Tiemann and Tigges, *ibid.*, 1900, **33**, 3713; Barbier and Bouveault, *Bull. soc. chim.*, 1896, [iii.], **15**, 1002.

[2] Tiemann, *Ber.*, 1898, **31**, 2901.

$$CH_2 : \underset{\displaystyle CH_3}{\underset{|}{C}} . CH_2 . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . COOH$$

Citronellic acid.
(I.)

$$(CH_3)_2C : CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . COOH$$

Rhodinic acid.
(II.)

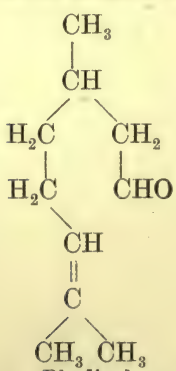
The literature of the subject is somewhat contradictory, and it does not seem necessary to go into the question in detail here.

When the ester of rhodinic acid is reduced by means of sodium and absolute alcohol it yields the corresponding alcohol[1] rhodinol—

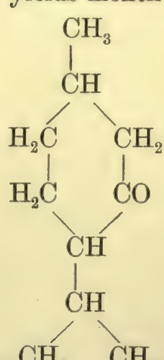
$$(CH_3)_2C : CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . CH_2OH$$

which is isomeric with citronellol. Here, again, the literature is contradictory, and it seems impossible to decide whether the two compounds are stereo-isomers or differ in structure.

Rhodinal,[2] the aldehyde corresponding to the alcohol rhodinol, is obtained by distilling together calcium formate and the calcium salt of rhodinic acid. Barbier and Bouveault regard it as having the structure (I.), because of its conversion into menthone. Citronellal, with which it is isomeric, when submitted to the action of acetic anhydride, is changed into isopulegol, as we have already described. On the other hand, rhodinal when treated in the same way yields menthone—



Rhodinal.
(I.)



Menthone.
(II.)

[1] Bouveault and Gourmand, *C. R.*, 1904, **138**, 1699.
[2] Tiemann, *Ber.*, 1898, **31**, 2902.

5. *Citral.*

By distilling together the calcium salts of formic and geranic acids we obtain the aldehyde citral.[1] Since this is a general reaction, the constitution of citral would probably be that shown in the equation below—

$$\begin{array}{l} \qquad\qquad\qquad\qquad\quad CH_3 \\ \qquad\qquad\qquad\qquad\quad \vert \\ (CH_3)_2C : CH.CH_2.CH_2.C : CH.COO-ca \\ \qquad\qquad\qquad\qquad\qquad H.COO-ca \end{array} = (CH_3)_2C : CH.CH_2.CH_2.\overset{\overset{\displaystyle CH_3}{\vert}}{C} : CH.CHO + CaCO_3$$

In support of this formula we may quote the decomposition of citral into acetaldehyde and methyl-heptenone, which takes place when the substance is warmed with a solution of sodium carbonate.

Citral, therefore, represents rhodinal or citronellal, from which two hydrogen atoms have been withdrawn; and differs from them further in that it contains no asymmetric carbon atom. But though it loses this possibility of isomerism, it retains another, for it has been found to occur in two geometrically isomeric forms[2]—

$$\begin{array}{rl} & H-C-CHO \\ & \quad\ \ \Vert \\ (CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2- & C-CH_3 \end{array}$$

Citral *a.*

$$\begin{array}{rl} & CHO-C-H \\ & \qquad\ \ \Vert \\ (CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2- & \quad\ C-CH_3 \end{array}$$

Citral *b.*

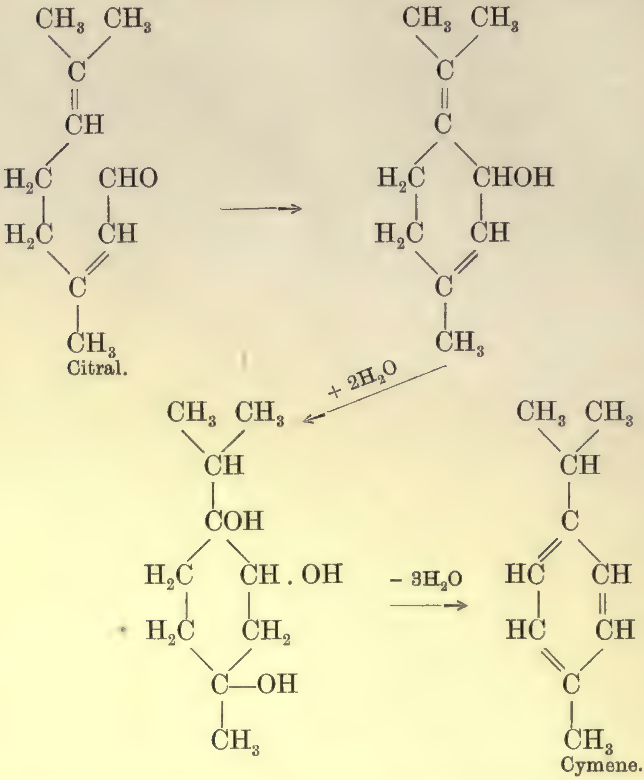
These have been shown by Harries and Himmelmann to be structurally identical; and the relative configurations have been deduced from the relations of the two compounds to geraniol and nerol, with which we shall deal later.

Like the other olefinic terpenes, citral can be converted into cyclic substances with great ease. When it is boiled for a long time with glacial acetic acid it is changed into cymene[3]—

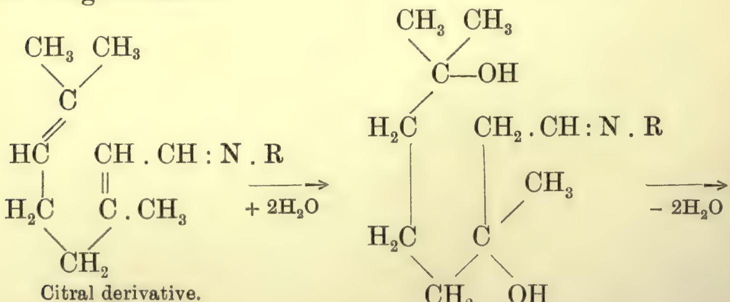
[1] Tiemann, *Ber.*, 1898, **31**, 827, 2899.

[2] *Ibid.*, 1899, **32**, 115; 1900, **33**, 877; Bouveault, *Bull. soc. chim.*, 1899, [iii.], **21**, 419, 423; Barbier, *ibid.*, 635; Kerschbaum, *Ber.*, 1900, **33**, 886; Zeitschel, *Ber.*, 1906, **39**, 1783; Harries and Himmelmann, *Ber.*, 1907, **40**, 2823.

[3] Tiemann and Semmler, *Ber.*, 1895, **28**, 2134.

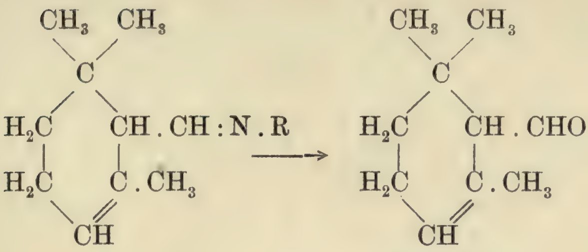


A second condensation of citral takes place when the aldehyde group is so treated that it takes no part in the action. For instance, if we condense citral with a primary amine, we obtain a cyclo-citral by a simple wandering of bonds and ring-formation—



Citral derivative. (I.)

(II.)

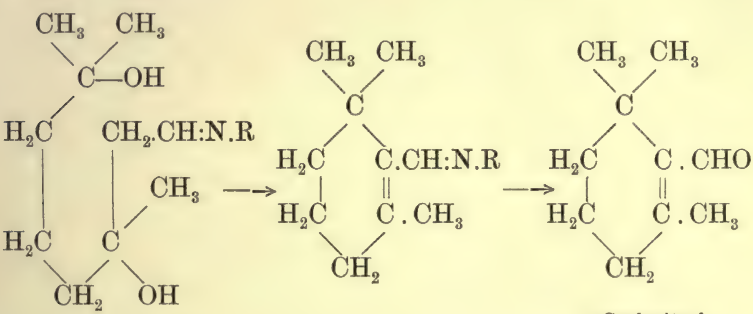


α-Cyclocitral.

(III.) (IV.)

The same result may be obtained by condensing citral with cyan-acetic ester instead of an amine. In each case, the amine or cyan-ester can be split off after the condensation to cyclocitral has taken place.

Cyclo-citral occurs in two isomeric forms,[1] the formation of either being dependent upon the manner in which water is eliminated from the molecule of an intermediate hydration product (II.). The formation of β-cyclocitral takes place as shown below—



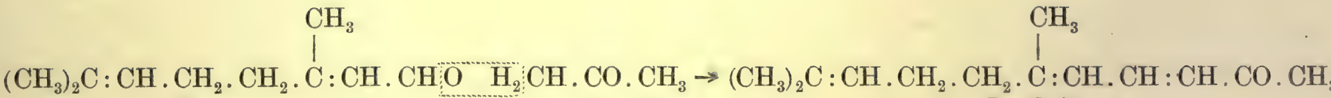
β-Cyclocitral.

(II.)

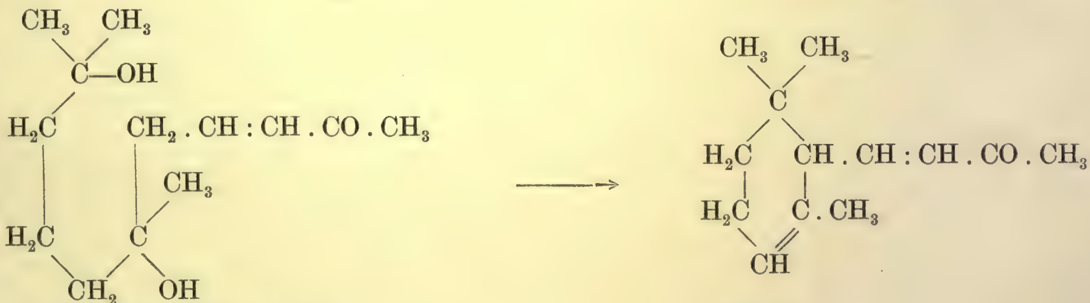
The practical interest of citral lies in the fact that when it is condensed with acetone by means of baryta, it yields a substance, pseudo-ionone, which, by the action of sulphuric acid, is changed into ionone,[2] the basis of artificial violet perfume—

[1] Tiemann, *Ber.*, 1900, **33**, 3719.

[2] Tiemann and Krüger, *Ber.*, 1893, **26**, 2691; Tiemann, *ibid.*, 1898, **31**, 808, 867, 1736, 2313; 1899, **32**, 827; Tiemann and Schmidt, *ibid.*, 1900, **33**, 3703.

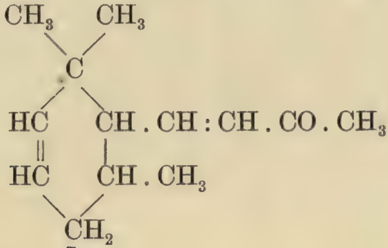


Citral. Acetone. Pseudo-ionone.



Pseudo-ionone hydration product. Ionone.

This body differs from the natural substance irone (to which the odour of violets is due) only in the position of a double bond—



Irone.

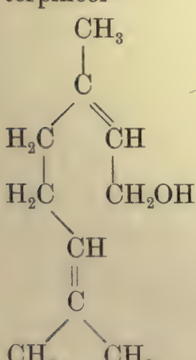
6. *Geraniol, Nerol, and Linalool.*

If we reduce citral with sodium amalgam in an alcoholic solution weakly acidified with acetic acid, a mixture of two isomeric alcohols, geraniol and nerol, is obtained. These two bodies, on oxidation, regenerate citral, and on this ground, as well as on account of other reactions common to both, it is assumed that they are structurally identical but stereoisomeric substances of the formula—

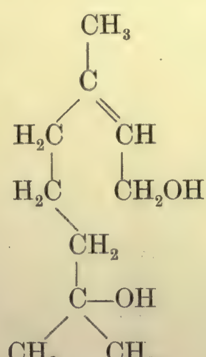
$$(CH_3)_2C : CH . CH_2 . CH_2 . \overset{\displaystyle CH_3}{\overset{|}{C}} : CH . CH_2OH$$

Proof of the correctness of this formula is afforded by the fact that when geraniol is heated with water to 150° C. it gives ethyl alcohol and methyl-heptenone; while on oxidation it gives acetone, lævulinic acid, and oxalic acid.

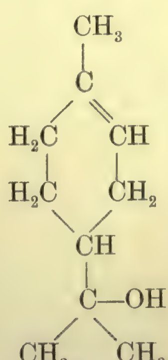
By the action of acetic acid, to which 1 or 2 per cent. of sulphuric acid has been added, both nerol and geraniol give terpineol—



Geraniol.



Hypothetical glycol.



Terpineol.

Now, this reaction takes place nine times faster with nerol than with geraniol; and if the two bodies are geometrical isomers, this difference allows us to draw a conclusion with regard to their configurations.[1] A comparison of the two formulæ below will suffice to show that in (I.) the groups which unite to form the terpineol ring are further apart in space than they are in (II.). The ring-formation will therefore occur more easily in the case of (II.) than in that of (I.). Hence we must ascribe to geraniol the first formula, and to nerol the second—

$$\begin{array}{l} \qquad\qquad\qquad\qquad\qquad\quad\;\; H—C—CH_2OH \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad\;\; \| \\ (CH_3)_2C : CH . CH_2 . CH_2—C—CH_3 \end{array}$$

Geraniol.

(I.)

$$\begin{array}{l} \qquad\qquad\qquad\quad CH_2OH—C—H \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad\;\; \| \\ (CH_3)_2C : CH . CH_2 . CH_2—C—CH_3 \end{array}$$

Nerol.

(II.)

We are now able to deal with the space formulæ of the two citrals. The oxidation of geraniol gives a mixture of citral *a* and citral *b*, in which citral *a* predominates; while with nerol the proportions are reversed, more citral *b* being formed. From this we may deduce that citral *a* has the same configuration as geraniol, while citral *b* has its groups arranged as in nerol—

$$\begin{array}{l} \qquad\qquad\qquad\qquad\qquad\quad\;\; H—C—CHO \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad\;\; \| \\ (CH_3)_2C : CH . CH_2 . CH_2—C—CH_3 \end{array}$$

Citral *a* (Geranial).

$$\begin{array}{l} \qquad\qquad\qquad\qquad\quad CHO—C—H \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad\;\; \| \\ (CH_3)_2C : CH . CH_2 . CH_2—C—CH_3 \end{array}$$

Citral *b* (Neral).

Both geraniol and nerol are found in nature as inactive substances, which agrees with the formulæ which we have ascribed to them above. The isomeric compound, linalool, however, occurs in both dextro- and lævo-rotatory forms, and must therefore contain an asymmetric carbon atom. The inactive form of linalool is convertible into both geraniol and nerol by the action of acetic anhydride. This reaction can be explained by assuming that linalool has the formula—

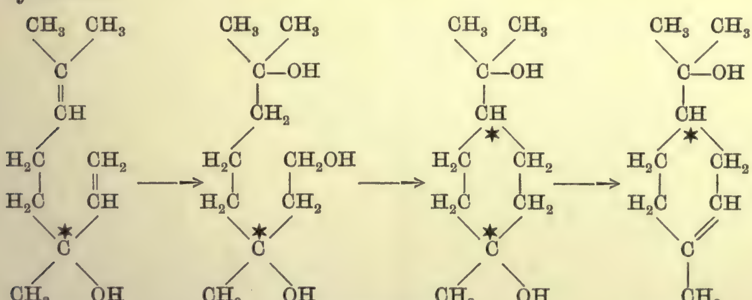
[1] Zeitschel, *Ber.*, 1906, **39**, 1780.

$$\begin{array}{c} \qquad\qquad\qquad\qquad\qquad\qquad\quad OH \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ (CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2 \,.\, C \,.\, CH : CH_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3 \end{array}$$

A comparison of the formulæ of geraniol, nerol, and this one proposed for linalool will show that by the addition of water to each of these substances we can produce in all three cases the same glycol of the formula—

$$\begin{array}{c} CH_3 \qquad\qquad\quad \\ | \qquad\qquad\qquad \\ (CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2 \,.\, C \,.\, CH_2 \,.\, CH_2OH \\ | \qquad\qquad\qquad \\ OH \qquad\qquad\quad \end{array}$$

This formation of a common hydration product suffices to explain the interconvertibility of the three isomers; but there is one point which seems to render the linalool formula rather doubtful. When we take lævo-linalool and treat it with acetic anhydride, terpineol is formed along with nerol and geraniol; and this terpineol is found to be dextro-rotatory. But when we compare the formulæ of terpineol and linalool, we find that the asymmetric carbon atom of linalool does not correspond to that in terpineol; in fact, the atom which in linalool was asymmetric is now not asymmetric, while a new asymmetric carbon atom has come into being. How optical activity can persist through such a change as this appears difficult to understand, unless we assume that it is a case of asymmetric synthesis.

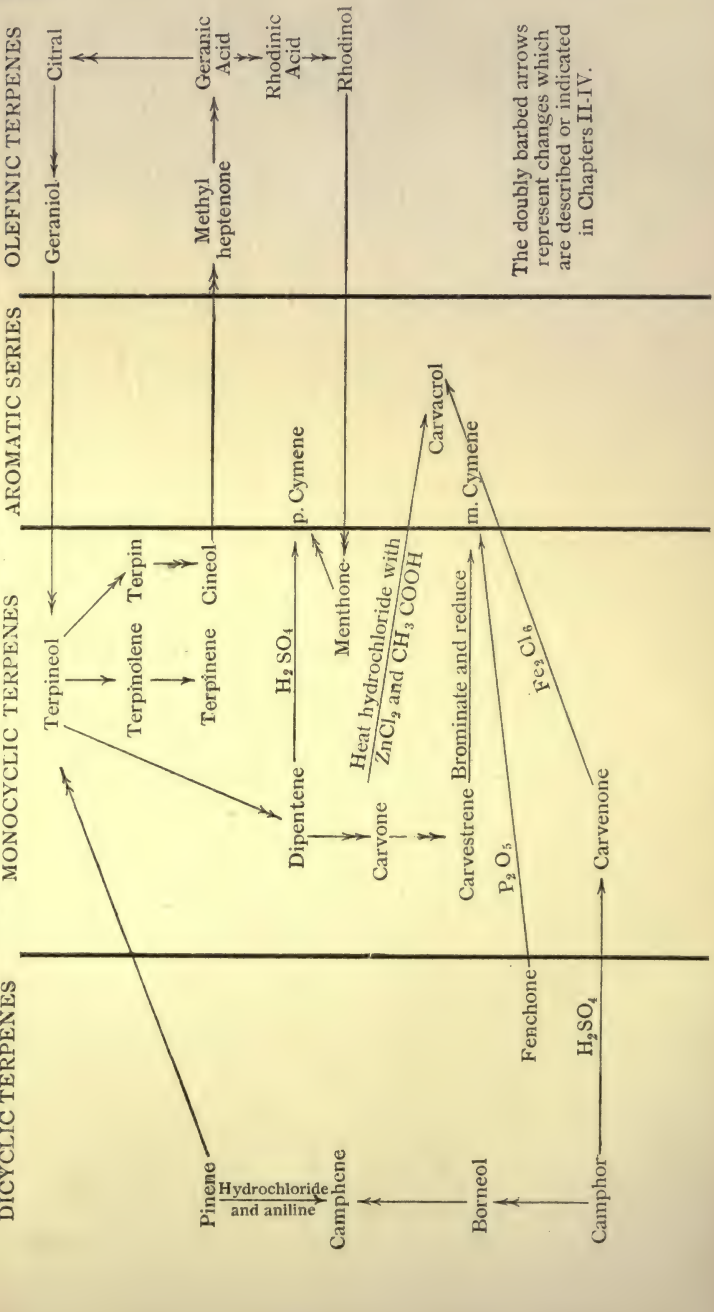


l-Linalool. Intermediate products. *d*-Terpineol.

This terminates our survey of the terpene class. In conclusion, we may append to this chapter a table showing some of the possible conversions of mono-cyclic, di-cyclic, and olefinic

terpenes into each other, and also into members of the benzene series.

Table showing some Relations between Terpenes & Benzene Derivatives.



CHAPTER V.

RUBBER.

1. Introductory.

The exact distribution of credit among the pioneers in the chemistry of rubber has in recent years produced a most unedifying amount of controversy;[1] and insinuations have been made by at least one German chemist which appear to overstep the bounds of normal scientific polemics. In these circumstances, it seems desirable to give an outline of the history of the subject in its earlier stages.

In 1860 Williams[2] observed that when rubber is distilled it yields what are now known as isoprene and dipentene. On leaving isoprene in a partly-filled bottle for some months, he noticed that it became oxidized and was converted into a viscid liquid. When this viscid material was distilled, at one point in the process the liquid solidified to "a pure white spongy elastic mass" which, when burned, gave off the characteristic odour of burning rubber. The material in question, on analysis, yielded the following results: 78·8 per cent. carbon, 10·7 per cent. hydrogen, and 10·5 per cent. oxygen. This composition corresponds to isoprene plus half a molecule of oxygen.

Bouchardat[3] in 1879 found that when hydrochloric acid solution is allowed to act upon isoprene, one of the products, after the reaction has proceeded for a fortnight or three weeks, is a non-volatile body having the composition C = 87·1 per cent., H = 11·7 per cent., and Cl = 1·7 per cent. If the chlorine be disregarded—and Bouchardat believed that its presence was

[1] For a complete account of this see Pond, *J. Amer. Chem. Soc.*, 1914, **36**, 165.

[2] Williams, *Phil. Trans.*, 1860, 245; *Proc. Roy. Soc.*, **10**, 516.

[3] Bouchardat, *Compt. rend.*, 1879, **89**, 1117.

due to contamination by foreign chlorinated compounds—these results agree closely with the formula $(C_5H_8)_x$. The substance thus produced "possesses the elasticity and other characteristics of rubber. It is insoluble in alcohol; it swells up in ether, also in carbon disulphide in which it dissolves in the manner of natural rubber." When submitted to dry distillation "it forms the same volatile hydrocarbons as rubber". "All these properties appear to identify this polymer of isoprene with the substance from which isoprene is formed, namely rubber."

Harries[1] has in recent times criticized this work of Bouchardat and has attempted to prove that Bouchardat's method does not yield the products described. Unfortunately for his contentions, he had read the original paper so carelessly that he apparently attempted a repetition of the work by the employment of hydrochloric acid *gas* whereas Bouchardat used aqueous hydrochloric acid. When an attempt is made to repeat an author's work it is usual to employ his own method; not to try a new one and then declare that the described method "seems almost excluded". Harries also[2] asserted that Bouchardat had not proved the identity of his product with true rubber. It is difficult to see what more Bouchardat could have done, considering the date at which he worked; and this attitude in the critic becomes more astonishing when it is recalled that in 1910-11 Harries made use of tetrabromides, nitrosites, and ozonides as tests to distinguish rubber; but in 1912-13 he discarded these as being inefficient, and concentrated his attention upon the rate of decomposition of the ozonides with water.[3]

The next stage in the history of synthetic rubber is marked by Tilden's paper of 1882.[4] Tilden showed that when turpentine vapour is passed through a red-hot tube, isoprene—

$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad C—CH=CH_2 \\ CH_2\diagup\!\!\!\diagup \end{array}$$

Isoprene.

[1] Harries, *Annalen*, 1913, **395**, 211.

[2] *Ibid.*, *Gummi-Zeitung*, 1910, **24**, 853.

[3] *Ibid.*, Lecture at Vienna, 12th March, 1910; *Chem. Zeit.*, 1910, **34**, 316; *Annalen*, 1913, **395**, 211.

[4] Tilden, *Chem. News*, 1882, **46**, 220.

is formed ; and he also stated that, by the action of nitrosyl chloride, isoprene was converted into rubber. Ten years later, Tilden[1] made public the fact that some isoprene which had been kept in a bottle for a long time had undergone change. "In place of the limpid colourless liquid the bottles contained a dense syrup in which were floating several large masses of solid, of a yellowish colour. Upon examination this turned out to be indiarubber." These original samples have now been tested by the ozone method and were found to be true rubber.[2] It may be noted that this work of Tilden's should be regarded as a real synthesis of rubber, and stands in a different category from Bouchardat's. Bouchardat obtained his isoprene by distilling rubber; so that his work consisted of *re-synthesizing* rubber from its decomposition products. Tilden, on the other hand, obtained his isoprene from turpentine, and may thus claim to have made a true synthesis of rubber.

Harries,[3] not having been able to repeat Tilden's work, contented himself with the statement that Tilden "never proved that he had rubber in his hands".

About 1899 or 1900, Kondakoff[4] showed that other members of the isoprene series could be converted into rubber-like materials by various methods.

In the earlier part of the present century, the uses of rubber were greatly extended; and as a natural consequence there was a marked effort to produce the material by artificial means on a manufacturing scale.

In 1909 Hofmann[5] discovered that isoprene may be converted into rubber by the action of heat. This is claimed as the first technical method of rubber synthesis. If it be a practical method, it appears curious that, during the war, many reports were current crediting Germany with smuggling rubber in from America via parcel post.

[1] Tilden, Paper read before the Philosophical Society of Birmingham, 1892.

[2] *Ibid.*, *Chemical Discovery and Invention in the Twentieth Century*, 1916 ; Pickles, *Trans.*, 1910, **97**, 1085.

[3] Harries, Vienna Lecture, 1910.

[4] Kondakoff, *On Synthetic Rubber* (in Russian) (1912) ; *J. pr. Chem.*, 1900, **62**, 175 ; 1901, **63**, 113 ; **64**, 109. See also Harries' Vienna Lecture and *Annalen*, 1911, **383**, 186.

[5] See Duisberg, *Eighth International Congress of Applied Chemistry*, 1912, **28**, 50, 86.

In 1908 a British syndicate quietly set to work upon the problem of the commercial synthesis of rubber.[1] A method of obtaining isoprene from fusel oil was worked out, thereby ensuring that the raw material should not be too expensive. In the course of some experiments, it occurred to Matthews to study the influence of sodium upon isoprene; and in July, 1910, he sealed the two substances up in a tube. Inspection of the tube in August showed that the contents had become viscid and contained a proportion of remarkably good rubber. The vessel was resealed and left till September, when it was found to contain a solid mass of amber-coloured rubber. A patent was applied for on 25th October, 1910.

Meanwhile Harries, the Badische Anilin und Soda Fabrik and Bayer and Co. were also at work, and the race was becoming a close one. Harries' story is as follows.[2] He claims that in February, 1910, he observed, during a purification of isoprene by distilling it over sodium, that the metal had an "altering" (verändernde) action upon the hydrocarbon. The fact that rubber-like materials resulted from the process was first established "in September or October," which is rather vague. He states that on 28th October, 1910, he verbally communicated his discovery to a representative of the Elberfeld Farbenfabriken in Berlin, and suggested that a patent should be taken out by them. This patent was applied for in Germany on 12th December, 1910, seven weeks after the British syndicate had applied for their English patent.

If we were to apply to Harries' story the same rigid scrutiny as he spent upon the work of Bouchardat and Tilden, the only evidence which we could regard as relevant would be the actual date of the patent application; as no corroboration has been offered for the other details.* In any case, under modern conditions, priority of discovery counts for less than priority of publication; and on that basis the Germans lost the race.

The controversy which arose out of this defeat was marked

[1] See Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

[2] Harries, *Annalen*, 1912, **395**, 211.

* The first scientific publication by Harries on the subject is dated 26th June, 1911 (*Annalen*, **383**, 188), and he there states (before the controversy arose) that he made the discovery at the *end* of 1910 (Ende des Jahres 1910).

by especial bitterness on the part of Harries;[1] and it is a matter for congratulation that chemical polemics are not usually conducted in that spirit. When a person devotes many pages to an attempt to demonstrate that German chemists have a prior claim to a subject, it seems peculiar to find him complaining against "the dragging in of nationalistic motives in scientific work". Before the war threw a flood of light upon German psychology, we should have been somewhat at a loss to comprehend this mental attitude.

2. The Properties and Constitution of Natural Rubber.

Natural rubber or caoutchouc is a transparent, tough elastic substance having no definite melting- or boiling-point.* It absorbs water, increasing in volume as it does so. It is soluble in several organic liquids, such as benzene, chloroform, carbon tetrachloride, dipentene, ligroin, and carbon disulphide. Its composition corresponds to the formula $(C_5H_8)_x$. It is unsaturated, combining readily with oxygen and chlorine; and it yields nitrosites and nitrosates with nitrous fumes. When distilled, it breaks down into a mixture of hydrocarbons of which the chief are isoprene and dipentene. When heated with sulphur or when treated with solutions of sulphur dichloride in carbon disulphide, it becomes "vulcanized," the process resulting in the rubber retaining its elastic properties over a wider range of temperature than when raw. When a high percentage of sulphur is introduced, vulcanite is produced.

Apart from the actions of halogens and nitrous fumes upon rubber, which have led to little, our knowledge of its constitution depends upon its behaviour with ozone.

Harries[2] states that when rubber is treated with ozone and the resulting ozonide is decomposed with water, the only isolable products are lævulinic aldehyde, lævulinic acid, and the peroxide of lævulinic aldehyde. The acid is evidently a secondary product of the reaction.

The molecular weight of the ozonide shows that its

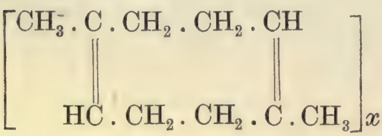
[1] Harries, *Annalen*, 1912, **395**, 211.

* It appears from some work of Harries that natural Para rubber occurs in at least three forms: oily, soluble, and insoluble.

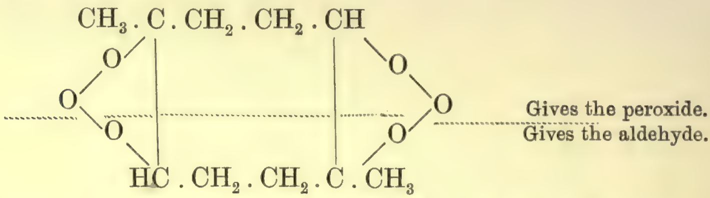
[2] Harries, *Ber.*, 1905, **38**, 1195.

composition is $C_{10}H_{16}O_6$, which points to the fact that the structure from which it was derived must have contained two double bonds, each of which has taken up one molecule of ozone.

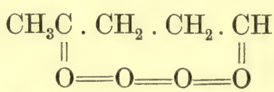
In order to account for these results, Harries has had to resort to an hypothesis which will hardly recommend itself to many chemists. He assumes, from the production of lævulinic aldehyde and its peroxide that rubber has the following structure:—



and that the ozonide has the constitution:—



The breakdown of the ozonide is supposed to take place along the dotted line, the lower half of the molecule producing lævulinic aldehyde, $CH_3 . CO . CH_2 . CH_2 . CHO$, whilst the upper half yields the peroxide:—



But at this point difficulties arise; for how can we suppose that the cyclo-octadiene ring can polymerize without destroying the double bonds in it? And if it does polymerize through the agency of the double bonds, how can they be left unchanged to attack the ozone molecules in order to produce the ozonide?

Harries endeavours to gain credence for his hypothesis by adducing the fact that cyclo-octadiene—which should be analogous to his assumed eight-membered ring—does actually polymerize readily; but inadvertently, no doubt, he omits to mention that one of the products of this polymerization is a di-cyclo-octadiene consisting of thin, pointed leaflets of m.p.

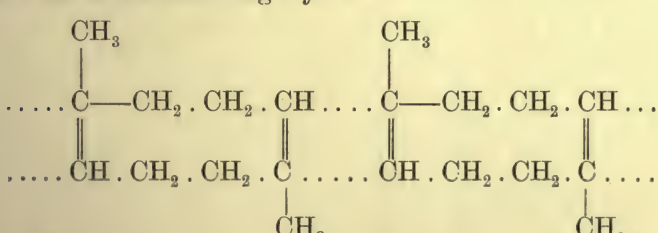
114° C.; whilst the other polymer is also a crystalline body.[1] The analogy with the properties of rubber is hardly close enough to support the eight-membered ring theory to any extent worth considering.

For his final demonstration of the presence of an eight-membered ring in the rubber molecule, Harries relied upon the following statements.[2] When the dihydrochloro-derivative of rubber is subjected to the action of pyridine,[3] he found that a substance *different* from rubber is regenerated.* On ozonizing this, he claimed to have isolated a cyclo-octadione derivative among the products. Therefore, according to his argument, the *original* rubber must have contained an eight-membered ring. The fallacy in reasoning is not worth dwelling upon, as it subsequently turned out[4] that he had made a "regrettable error"† and had mistaken an open-chain di-ketone,

$$CH_3 . CO . CH_2 . CH_2 . CH_2 . CO . CH_3,$$

for a cyclo-octadione derivative. It seems hardly worth while to comment on the value of such evidence; though Harries still contends that it establishes the presence of an eight-membered ring in the rubber molecule.

Harries[5] proposes to regard the polymerization of the eight-membered rings as a mere kind of loose addition, so that the polymer breaks down into cyclo-octadiene molecules under the influence of ozone. In other words he regards rubber as being built up from a large number of separate cyclo-octadiene molecules clinging together by means of Thiele's partial valencies, somewhat in the following style:—



[1] Willstätter and Veraguth, *Ber.*, 1905, **38**, 1975.

[2] Harries, *Ber.*, 1913, **47**, 2590. [3] *Ibid.*, 733.

* "Dieser (the regenerated substance) ist nicht mehr identisch mit dem natürlichen Kautschuk."

[4] Harries, *Ber.*, 1914, **48**, 784. † "Ein bedauerlicher Irrtum."

[5] Harries, *Ber.*, 1905, **38**, 1195, 3985.

Pickles[1] has adduced several reasons why this conception should not be accepted without further evidence. In the first place, if ozone has the faculty of depolymerizing this peculiar compound, there appears to be no reason to deny the same depolymerizing power to other reagents. On this basis bromine would first break down the colloidal rubber to independent cyclo-octadiene derivatives, and would then produce a simple tetrabromo-compound of the following structure:—

$$\begin{array}{lllll} CH_3 . CBr & — CH_2 & — CH_2 & — CHBr & \\ \quad\quad\;\; | & & & \quad\; | & \\ \quad\quad\;\; CHBr & — CH_2 & — CH_2 & — CBr . CH_3 & \end{array}$$

In actual practice the bromo-derivative of rubber appears to have a composition which is probably as complex as that of rubber itself.*

Again, nitrous fumes might be expected to behave in a manner similar to ozone, but their action on rubber, as studied by Harries himself, results in complicated substances whose formulæ,† established by molecular weight determinations, are $C_{20}H_{30}O_{14}N_6$ and even $C_{40}H_{62}O_{24}N_{10}$.

Yet another objection to the physical polymerization idea is to be found in the behaviour of rubber on heating. Under ordinary pressure the heating of rubber produces all the effects found when a complex substance undergoes complete disruption; whilst if the heating takes place under reduced pressure, cyclo-octadiene derivatives are not formed, but it is found that the smallest molecule in the distillate contains at least twenty carbon atoms.‡

This does not exhaust the evidence against Harries' idea; but it is sufficient to indicate some of the weak points of his hypothesis.

Pickles proposes a formula which certainly avoids these difficulties. He suggests that rubber consists of long chains built up from the group C_5H_8 by normal polymerization:—

[1] Pickles, *Trans.*, 1910, **97**, 1085.

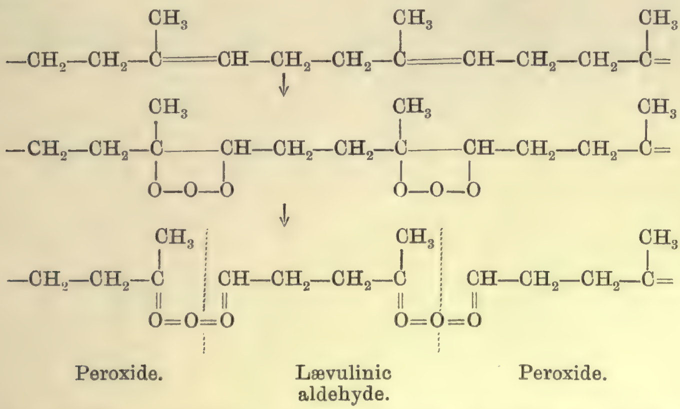
* Harries (*Annalen*, 1911, **383**, 227) endeavours to get round this by suggesting that the bromo-derivative is an adsorption-compound, an hypothesis for which he adduces no evidence.

† Harries (*ibid.*) asserts, in reply to this, that most terpene nitrosites are bimolecular, which would reduce the rubber nitrosite to $C_{10}H_{15}O_7N_3$, thus making the C_8 ring possible.

‡ Harries makes no reply to this argument.

$$\ldots\underset{\substack{|\\ \mathrm{CH_3}}}{}\!\!\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}{=}\mathrm{CH}{-}[\mathrm{CH_2}]_2{-}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}{=}\mathrm{CH}{-}[\mathrm{CH_2}]_2{-}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}{=}\mathrm{CH}{-}[\mathrm{CH_2}]_2{-}\ldots\ldots$$

The oxidation results require that the two ends of the chain should be linked together; and Pickles assumes that at least eight C_5H_8 complexes are included in a ring. To account for the ozone results, Pickles proposes the hypothesis that after the formation of the ozonide, the linkage between the carbon atoms is ruptured whilst the ozonide chain remains intact till later :—



This proposal certainly throws less strain upon the chemist's credulity than is demanded by Harries' hypothesis.

3. The Anglo-French Synthesis of Artificial Rubber.

In devising a manufacturing process on a large scale, the first point to be considered is the possible supply and price of the raw material involved.[1] A synthesis of rubber on a commercial scale might imply a demand running up to 100,000 tons; and before proceeding further it is necessary to make sure that this demand can be filled without producing a shortage in the raw material.

Turpentine appeared at first sight to be a suitable starting-point; but the imports of that substance into this country in the years previous to 1910 were found to average less than

[1] For a complete account of the history of the syndicate's work, see Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

29,000 tons per annum; so that the additional demand for three times that quantity would disturb the market and cause a rise in price which it would be difficult to estimate. Acetone was also ruled out by the question of cost; since, in order to compete with natural rubber, the artificial substitute must be manufactured at a price not exceeding one shilling per pound.

The choice of the syndicate fell upon starch, which was readily obtainable at a low price. An alliance was made with Fernbach, of the Pasteur Institute, and this investigator worked out a fermentation process whereby starch (from maize or potatoes) is convertible into fusel oil by one method and into acetone by another. The fusel oil thus obtained is found to contain an exceptionally high percentage of butyl alcohol.

The next stage in the process consists in treating the butyl alcohol with hydrochloric acid gas, whereby it is converted into butyl chloride.

By the action of chlorine, a mixture of dichloro-derivatives is obtained from the butyl chloride. The apparatus used in this conversion consists of a boiler to which is attached a Young's fractionating column to retain in the boiler all the higher-boiling constituents of the mixture when formed. The butyl chloride vapour passes from the boiler up to a chlorinating chamber where it meets a stream of chlorine; and the reaction between the two is accelerated by the action of light. A second condenser attached to the reaction chamber prevents the escape of the products. Any dichloro-derivative that is formed drops back through the Young column and is retained there; whilst fresh supplies of the lower-boiling butyl alcohol rise up to take its place in the reaction chamber. The formation of higher substitution products is thus avoided. In this way a mixture is obtained containing $CH_3CH_2CHCl \cdot CH_2Cl$; $CH_3 \cdot CHCl \cdot CH_2 \cdot CH_2Cl$; and $CH_2Cl \cdot CH_2 \cdot CH_2 \cdot CH_2Cl$.

Contrary to what might have been expected, these substances when passed over heated soda-lime all give rise to the same product: butadiene, $CH_2 : CH \cdot CH : CH_2$. Apparently intramolecular change takes place in the case of 1 : 2-dichlorobutane, or its product, under the action of the soda-lime.

The final stage, conversion of the butadiene into artificial rubber, is carried out by allowing the hydrocarbon to stand

in contact with a small quantity of sodium, the length of time required ranging from hours to weeks and depending on the temperature conditions.

It is claimed that by this process artificial rubber may be manufactured at from 4d. to 6d. per lb., as the raw materials are all cheap.

Synthetic rubber is apparently not yet on the market (1918) owing to the fact that during the war the plant has been employed for the production of acetone for munitions instead of butyl alcohol.

Another method of obtaining an artificial rubber has been suggested by Perkin, starting from amyl alcohol. This is first converted into amyl chloride; the latter is then chlorinated, as in the case of butyl alcohol, producing a series of dichloro derivatives, which, when passed over heated soda-lime, yield isoprene—

$$\begin{matrix} CH_3\diagdown \\ CH_2\diagup\!\!\!\diagup \end{matrix} C{-}{-}{-}CH{=}CH_2 \quad .$$

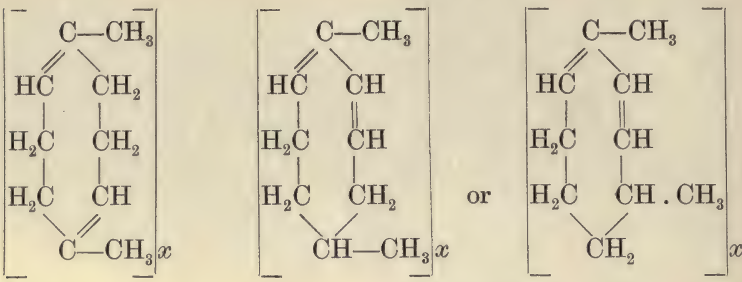
By treatment with metallic sodium, the isoprene polymerizes to an artificial rubber, different in constitution from the butadiene rubber, but equally valuable commercially.

4. Natural Rubber and the Artificial Rubbers.

It must be clearly borne in mind that the artificial or synthetic rubbers, though they have all the useful properties of the natural substance, are not necessarily identical with it in chemical constitution. Some of them, as is evident from their raw materials, are obviously different; whilst even in the case of isoprene polymers we cannot safely assert that their identity with natural rubber is proved.[1]

Harries[2] states that the autopolymerization of isoprene gives rise in the main to what he calls a "normal" product; but that along with this is formed, in small yield, a different substance. On his ring-hypothesis the formulæ of these bodies are as shown below:—

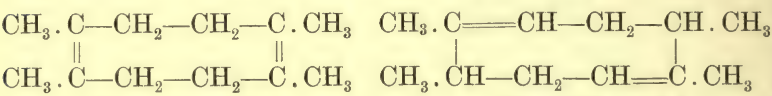
[1] See Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 1071.
[2] Harries, *Annalen*, 1911, **383**, 184.



Normal form. By-product.

The proof adduced in favour of the by-product structure is that he thinks he isolated methyl-glyoxal among the decomposition products of the ozonide.*

In the case of the polymer of dimethyl-butadiene, two ozonides were obtained which, on decomposition, yielded acetonylacetone and some strong reducing substances. From this Harries deduced that along with the "normal" polymer in this case there must be produced another which yields the reducing material, assumed by him to be a keto-aldehyde. For the two forms which he imagines exist he has devised the following formulæ which may possibly be established when any definite evidence in their support is produced :—



Normal form giving Acetonylacetone. By-product giving a Keto-aldehyde.

Further results were given in a later paper.[1] An examination of the rate of decomposition of various ozonides was carried out by the following method. About 10 grammes of the ozonide were suspended in 100 grammes of water and heated under a reflux to 120°-125° C. Every quarter (or half) hour the mixture was shaken until the ozonide stuck to the walls of the vessel; the clear liquid was then poured off; the vessel and ozonide were dried for some hours *in vacuo* and then weighed; the decanted liquid was poured back and a fresh experiment begun. From the loss of weight in the ozonide the amount of decomposition was calculated.

* "Unter diesen wurde ein Produkt festgestellt, welches ich für Methylglyoxal ansprechen möchte."

[1] Harries, *Annalen*, 1912, **395**, 211.

Harries states that the rates of ozonide decomposition were similar for natural rubber and for autopolymerized isoprene. Divergency was noted in the case of a rubber obtained from piperylene, $CH_3 . CH : CH . CH : CH_2$, which is not astonishing in view of the fact that piperylene-rubber gives ozonide decomposition products differing entirely from those of natural rubber.

The decomposition curves of the ozonides derived from the rubbers obtained by the sodium-polymerization process differ, according to Harries, from the curve for the ozonide of natural rubber; but it must be noted that he himself points out that even natural rubbers differ among themselves in the readiness with which they form ozonides.

The same method has been applied to the case of synthetic 1 : 5-cyclo-octadiene; and Harries states that its ozonide breaks down at almost exactly the same rate as the ozonide of butadiene-rubber. From this he claims to have proved that his eight-membered ring hypothesis is correct; but it appears that if Pickles' postulates as to the structure of the ozonide were applied to this case the argument for his formula would hold just as well. The matter must therefore be regarded as *sub judice*, the more so since the real value of the decomposition-velocity method is by no means thoroughly tested yet.

Ostromisslenski[1] has obtained by the polymerization of vinyl bromide a material which he terms caouprene bromide. This exists in three forms $\alpha \rightarrow \beta \rightarrow \gamma$ which, when submitted to the action of ultra-violet light, are capable of change in the direction shown by the arrows. Boiling with anhydrous acetic acid has a similar effect. The bromide of Harries' butadiene-rubber, which also exists in three modifications, is either identical or isomeric with caouprene bromide. Ostromisslenski does not accept Harries' eight-membered ring hypothesis, but regards caouprene bromide as constituted in the following manner :—

$$\begin{array}{llll} CH_2\text{——}CHBr\text{—}CH_2\text{—}CHBr\text{—}CH_2\text{——} & CHBr & & \\ | & | & & \\ CHBr\text{—}CH_2 \ldots\ldots\ldots\ldots\ldots\ldots & CHBr\text{—}CH_2 \ldots & & \end{array}$$

where the dotted line represents an unknown number of $—CH_2 . CHBr—$ groups.

[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 204.

Both caouprene bromide and butadiene-rubber bromide, when treated with zinc dust, yield the same rubber, apparently butadiene-rubber.

Lebedeff[1] has investigated the polymerization of derivatives of divinyl which contain conjugated double bonds; and he finds that the reaction-products contain cyclo-hexene derivatives as well as resinous material which contains a cyclo-octadiene system. The relative amounts of the two materials produced appear to depend upon the conditions. Low temperatures and the action of light favour the formation of cyclo-octadiene derivatives; whilst cyclo-hexene compounds are produced at higher temperatures. Cyclo-butane derivatives are formed from substances of the allene type.

It will be seen that our knowledge of the constitutions of natural and artificial rubber is still meagre in the extreme.

5. Conclusion.

The foregoing sections will have made clear that the chemistry of rubber is still in a very uncertain condition; and it may be well to summarize the main facts here.

Natural rubber is not a definite chemical individual, but varies in properties according to the locality from which it is procured, and even a single sample may contain three different types of "rubber". Artificial rubber, like the natural substance, includes various classes of material which appear to differ from one another according to the manner in which they are prepared.

The first definite synthesis of an artificial rubber was carried out by Tilden through the spontaneous polymerization of isoprene. Later work has shown that isoprene and its homologues may be polymerized by heat or by the action of sodium. The "sodium-rubbers" have chemical properties different to a slight extent from the autopolymerization products; but both classes show all the physical characteristics of rubber.

The synthesis of artificial rubber on a commercial scale has been worked out by an Anglo-French syndicate, the raw material being starch, which is converted by fermentation

[1] Lebedeff, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 949; 1911, **43**, 820.

into butyl alcohol and thence, by chlorination and removal of hydrochloric acid, into butadiene, which is finally polymerized to artificial rubber by the catalytic action of sodium.

On heating, rubber is broken down to isoprene.

Rubber, by the action of ozone and subsequent decomposition of the ozonide with water, yields lævulinic aldehyde and lævulinic aldehyde peroxide.

On the basis of this last reaction, Harries has proposed the hypothesis that rubber contains an eight-membered ring and that a large number of these cyclic molecules are loosely hung together by partial valencies to form the colloid which we know. Pickles has suggested that the rubber molecule is a true chemical molecule containing a cyclic structure comprising a large number of carbon atoms. Some of the experimental facts agree with either view. It is clear that we are still a considerable distance from the definite proof of the constitution of rubber.

CHAPTER VI.

THE ALKALOIDS.

A.—General.

When we attempt to define what we mean by the term "alkaloid" our difficulties are not small. On the one hand, our definition may be so drawn as to include almost every naturally occurring nitrogen-compound, which is obviously useless as a mode of classification; or it may be so narrow as to exclude some of the most important of the substances which are usually included in the alkaloid group. The most general definition is perhaps the best; and for our present purpose we shall treat as alkaloids those naturally occurring substances which contain cyclic chains, of which at least one member is a nitrogen atom. This definition opens to us a much wider field than we can possibly attempt to cover in the space at our disposal, and in the following pages we shall aim at describing the syntheses and constitutions of a few typical compounds rather than at a survey of the whole subject.

Practically all the important alkaloids are found in the tissues of vegetables; and if we except xanthine derivatives, we might have modified the definition given above by limiting the term "alkaloid" to basic substances found in plants.

As the following pages will show, the chemistry of the alkaloids resembles that of the aromatic compounds, in that each class seems to be built up upon the basis of one substance. In the aromatic series benzene lies at the root of all the compounds, however complicated they be; whilst in the alkaloids pyridine appears to be equally essential. And just as among the aromatic types we find a benzene ring condensed with other cyclic chains, so in the alkaloids we may discover compounds in which the pyridine ring is overlaid with others. Even the derivatives of the purine group may be considered to

be derived from pyridine by the substitution of a second nitrogen atom in the ring.

According to Guareschi,[1] the alkaloids are the degradation products of protoplasmic action in plants. They do not seem to be again assimilated by the plant once they are formed, but remain in the saps in the same way as uric acid may remain in the human tissues. Pictet[2] has dealt with the subject in some detail, and we may here summarize his views.

In the first place, he believes that alkaloids are not produced in plants by direct syntheses, but are rather to be regarded as the decomposition products of much more complicated substances. But as soon as the alkaloid is formed in the plant, it immediately reacts with some other plant product to form a derivative. For example, some alkaloids, such as soline, are glucosides as well as alkaloids; so that it is probable that in their case the first-formed alkaloid reacts with glucose within the plant-tissues. A more usual case, however, is that in which the alkaloid condenses with an organic acid, as in the case of cocaine or atropine. But by far the commonest case of all is that in which the alkaloid reacts with an alcoholic radicle, usually methyl alcohol, to form an ether. In this class of derivatives the action of formaldehyde apparently lies at the root of the syntheses. Alkaloids which contain a pyrrol ring are possibly derived from proteins; and it is noteworthy that while on the one hand Fischer has shown that albumen on hydrolysis gives pyrrol derivatives, it has been proved by Nencki, Küster, Zaleski, and Marchlewski that the same nucleus is to be found in hæmoglobin and chlorophyll.

With regard to the occurrence of the alkaloids in nature, very little generalization is possible. The monocotyledons seem to be the richest in members whose tissues produce these substances; while among the cryptogamia there appears to be no alkaloid formation. Just as little regularity is found with regard to the distribution of the alkaloids in the various portions of the plants themselves. Though no general rule can be formulated, it seems probable that alkaloids are most often found in the fruits and sap, or, in trees, in the bark.

[1] Guareschi, "Alkaloide," p. 414.

[2] Pictet, *Arch. soc. phys. nat. Genève*, 1905, IV., **19**, 329; *Arch. d. Pharm.*, 1906, **244**, 389.

Since in most cases alkaloids occur as salts, they are obtained from the actual plant tissues by the action of alkali, which liberates the basic part of the molecule. If this be volatile in steam, the alkaloid is obtained in this way; but if it be not thus volatile it is extracted from the tissues by treating them with acids, which dissolve the alkaloids, forming solutions of their salts, from which the free alkaloid is obtained by the action of alkali. Final purification is carried out by crystallization of the alkaloid or of its salts. When extraction is carried out on a small scale, chloroform is often used to remove alkaloids from the tissues in which they occur.

The majority of alkaloids are solid substances, but one or two are liquids which can be distilled without decomposition. Nearly all of them have powerful actions upon the animal organism; but owing to our ignorance of the relation between chemical constitution and physiological action, not much can be said on the subject. In most cases alkaloids are found to possess lævo-rotation, and it is very seldom that both optically active forms are found in nature.

B.—Methods Employed in the Determination of Alkaloid Constitutions.

After we have carried out an elementary analysis of an alkaloid we are in a position to state its percentage composition, and by a molecular weight determination we can estimate the number of atoms which its molecule contains. The next step is the determination of the mode in which these atoms are linked together in the alkaloid molecule, and we shall now give a brief account of some common reactions which are employed to solve this problem.

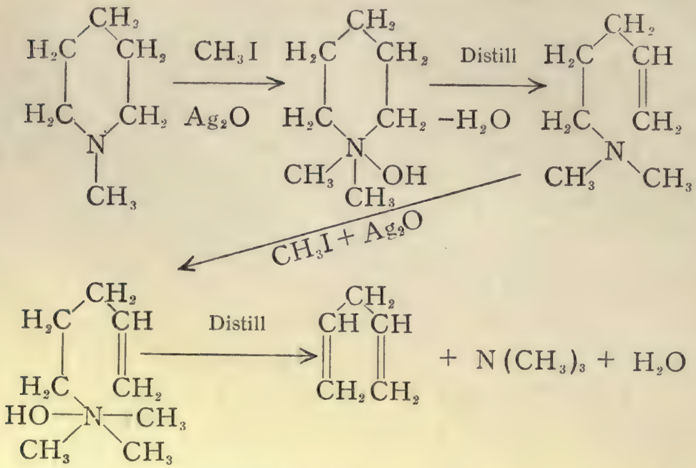
In the first place, since many alkaloids are known to be esters, it is usual to employ some hydrolytic method in order to see whether or not the alkaloid molecule can be decomposed into some simpler grouping. To this end the alkaloid may be heated with water, acids, or alkalis until it is decomposed into its component acid and base. This method, while breaking up any salt or ester, does not, except in a few cases, result in any further destruction of the body; so that from the constitutions of the two halves we are able to deduce the constitution of the parent substance.

This method of decomposition, however, may not carry us far enough, and it is usually seconded by a more violent action. For instance, the alkaloid may be fused with alkali, distilled with zinc dust, heated with bromine or phosphoric acid. When reagents such as these are employed, the less durable part of the molecule is usually shattered; and in the reaction-product we find some stable nucleus such as pyridine, quinoline, or isoquinoline, from which the whole alkaloid is derived.

Again, many alkaloids exist in the form of methyl ethers. These can be broken up by boiling with hydriodic acid (Zeisel's method); and by passing the methyl iodide thus formed into silver nitrate solution the number of methyl radicles split off by the hydriodic acid may be estimated, and thus the number of methoxyl groups in the alkaloid can be ascertained.

When the alkaloid contains an oxygen atom, it is of importance to determine whether this occurs in a carbonyl, carboxyl, hydroxyl, or ether group. The first is determined in the usual way by the action of phenylhydrazine or hydroxylamine; the hydroxyl group can usually be detected by acylating it or by the action of dehydrating agents, which split off water and leave an unsaturated substance; while if the alkaloid is an alkyl ether it can often be decomposed by Zeisel's method. If the carboxyl group occurs in the alkaloid under examination, there is not much difficulty in detecting its presence.

All alkaloids contain nitrogen, but it is necessary to discover in what way this nitrogen is linked with the rest of the molecule. Herzig and Meyer have devised a method of determination for methyl-imino groups which is very useful in this branch of research. The hydriodides of bases in which a methyl group is attached to nitrogen, when heated to about 300° C., split off methyl iodide, which can be estimated with silver nitrate just as in the case of the methoxyl group. A somewhat similar decomposition results in the reaction which is usually termed "exhaustive methylation". Here, by the action of methyl iodide and silver oxide, assisted by dry distillation, a cyclic nitrogen compound may be made to lose its nitrogen atom with but little alteration in the rest of the molecule. The formulæ will make the process clear without further explanation :—



The final stages in the constitution determination of any alkaloid are usually those in which the oxidation products of the substance are studied. We need not describe the actions of the various agents employed, as they are all well known. The most useful are potassium permanganate, hydrogen peroxide, dilute nitric acid, and chromic acid.

We must now proceed to the examination of the evidence which has been collected with regard to the synthesis and constitutions of some alkaloids.

C.—The Pyridine Group.

Piperine.

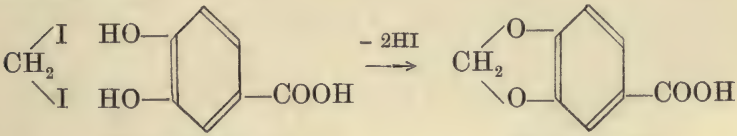
When the alkaloid piperine is boiled with alcoholic potash it is decomposed into piperidine and piperic acid.[1] The constitution of piperidine is established by the Ladenburg synthesis from pentamethylene diamine, as well as by the formation of piperidine from pyridine, by reduction. We have, therefore, only to determine the constitution of piperic acid in order to establish the constitution of piperine.

The decomposition of piperine may be expressed in the following way:—

$$\underset{\text{Piperine.}}{C_{17}H_{19}O_3N} + H_2O = \underset{\text{Piperidine.}}{C_5H_{11}N} + \underset{\text{Piperic acid.}}{C_{12}H_{10}O_4}$$

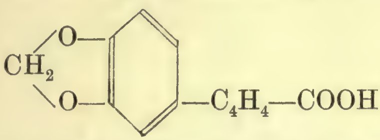
[1] Babo and Keller, *J. pr. Ch.*, 1857, **72**, 53.

Fittig, by the action of permanganate, oxidized piperic acid to an aldehyde, piperonal, which has the composition $C_7H_5O_2 . CHO$. On further oxidation, piperonal is converted into the corresponding acid, piperonylic acid, $C_7H_5O_2 . COOH$. Now, this substance can be synthesized by the action of methylene iodide upon protocatechuic acid in presence of caustic potash, and therefore it must be the methylene ether of that acid :—

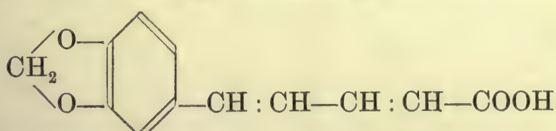


Protocatechuic acid. Piperonylic acid.

By subtracting the atoms in piperonylic acid from those which make up piperic acid, we find a surplus of four carbon and four hydrogen atoms. This —C_4H_4— must be so attached to the benzene ring of piperonylic acid that on oxidation it disappears entirely and does not give rise to a second carboxyl group in the molecule. The only way in which this condition can be fulfilled is by inserting the group —C_4H_4— between the carboxyl group and the benzene ring of piperonylic acid. Piperic acid would thus be represented by—



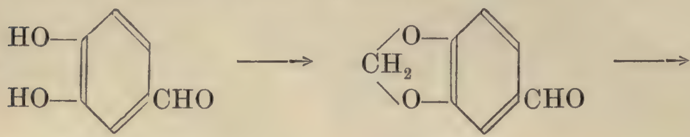
When piperic acid is allowed to react with bromine, it takes up four atoms of the halogen, thus showing that it contains two double bonds. These double bonds must be in the side-chain between the nucleus and the carboxyl group, hence we may ascribe the following formula to piperic acid :—



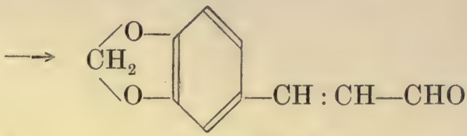
The synthesis of piperic acid may be carried out in the following way. Synthetic protocatechuic aldehyde[2] was

[1] Fittig and Remsen, *Annalen*, 1871, **159**, 142.
[2] Tiemann and Koppe, *Ber.*, 1881, **14**, 2015.

converted by methylene iodide and potash into piperonal,[1] which, when warmed with acetaldehyde and very dilute alkali (Claisen's reaction), forms piperonyl-acrolein—

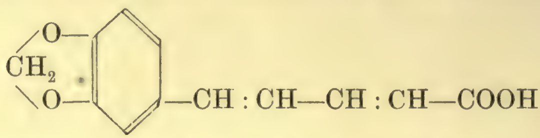


Protocatechuic aldehyde. Piperonal.

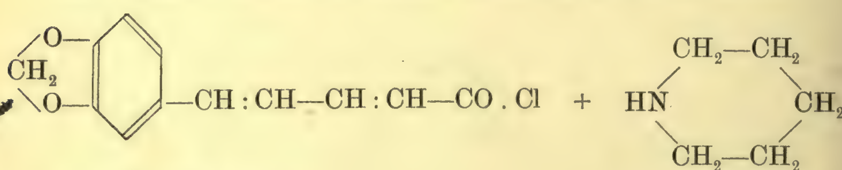


Piperonyl-acrolein.

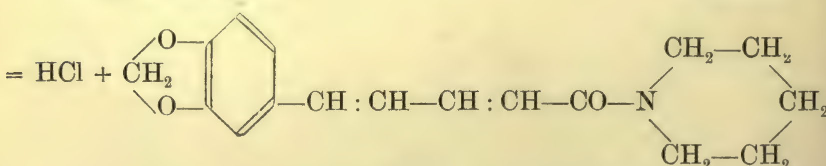
When this acrolein derivative is heated for several hours with sodium acetate and acetic anhydride it condenses with a molecule of acetic acid (Perkin's reaction), and forms piperic acid[2]—



By converting piperic acid into its chloride and heating the latter with piperidine in benzene solution, piperine is formed.[3]



Piperic acid chloride. Piperidine.



Piperine.

[1] Wegscheider, *Monatsh.*, 1893, **14**, 382.
[2] Ladenburg and Scholtz, *Ber.*, 1894, **27**, 2958.
[3] Rügheimer, *Ber.*, 1882, **15**, 1390; Fittig and Remsen, *Annalen*, 1871, **159**, 142.

In this way the alkaloid can be synthesized, its constitution being proved by the synthesis and further certified by the decomposition reactions which we have mentioned.

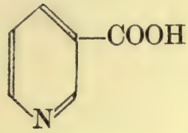
D.—The Pyrrolidine Group.

1. *Nicotine.*

The alkaloid nicotine stands in a position midway between the pyridine and the pyrrolidine groups; for, as will be shown presently, it contains both a pyridine and a pyrrolidine nucleus. It therefore forms a convenient bridge by which we can pass from the consideration of the one class to the other.

Nicotine is a basic substance having the composition $C_{10}H_{14}N_2$. Its constitution has been established by means of the following reactions:—

1. Nitric acid, chromic acid, or potassium permanganate oxidize nicotine [1] to nicotinic acid—



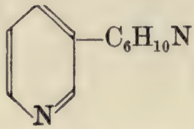
2. By the action of bromine upon nicotine, two derivatives [2] are formed—

 (*a*) Dibromocotinine, $C_{10}H_{10}Br_2N_2O$.
 (*b*) Dibromoticonine, $C_{10}H_8Br_2N_2O_2$.

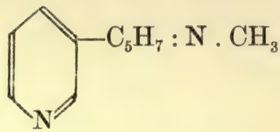
3. When dibromocotinine is decomposed by bases it gives methylamine, oxalic acid, and a compound C_7H_7NO. By the same treatment dibromoticonine yields methylamine, malonic, and nicotinic acids.
4. Nicotine is a di-tertiary base,[3] giving two isomeric methyl iodide addition products.

[1] Huber, *Annalen*, 1867, **141**, 271; Weidel, *Annalen*, 1873, **165**, 328; Laiblin, *Ber.*, 1877, **10**, 2136.
[2] Pinner, *Ber.*, 1893, **26**, 292.
[3] Pictet and Genequand, *Ber.*, 1897, **30**, 2117.

From the first reaction it is obvious that nicotine must be pyridine, with a side-chain in the β-position.



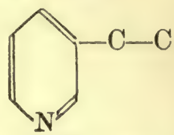
From the third reaction it is clear that of the two nitrogen atoms in nicotine, one carries a methyl group. This one cannot be the pyridine nitrogen. Further, the second nitrogen atom (which *does* carry the methyl radicle) cannot belong to a pyridine ring. We may thus go a step further, and represent nicotine by the formula—



Again, the third reaction shows us that dibromocotinine and dibromoticonine give rise to three carbon chains—

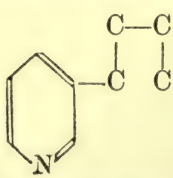
C—CH_2—C
Malonic acid chain.

—C . C—
Oxalic acid chain.



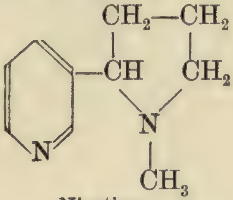
C_7H_7NO chain.

These must be somehow combined in the nicotine molecule, so we may write the nicotine skeleton thus—



To this we must attach the group : = N . CH_3 in some way. From the fourth reaction we deduce that this nitrogen atom is a tertiary one, so that the two isomeric methyl iodide addition products may be explained by the addition of methyl iodide to a different nitrogen atom in each case. But if the group : N . CH_3 is to contain a tertiary nitrogen atom, and also to be attached to the nicotine skeleton given above, the only way is

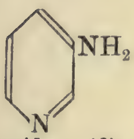
to make the nitrogen atom a member of a ring. The constitution of nicotine would then be—



Nicotine.

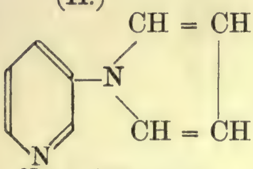
The synthetic preparation of nicotine proved to be a much harder task than was anticipated. The first steps were taken by Pictet and Crépieux,[1] who, by heating *β*-amido-pyridine (I.) with mucic acid, were able to produce (II.) N-*β*-pyridyl-pyrrol. Like many other N-alkyl derivatives of pyrrol, this substance when passed through a heated tube undergoes a molecular rearrangement, in the course of which the pyridine group is transferred to the carbon atom next the nitrogen in the pyrrol ring. The compound thus formed is *αβ*-pyridyl-pyrrol (III.)—

(I.)



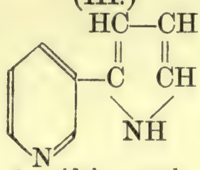
β-amido-pyridine.

(II.)



N-*β*-pyridyl-pyrrol.

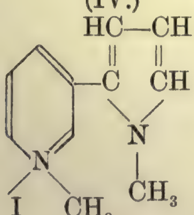
(III.)



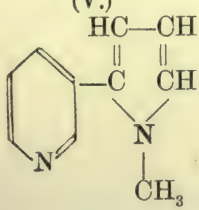
β-pyridyl-*α*-pyrrol.

From this substance Pictet[2] continued the synthesis in the following way. The *αβ*-pyridyl-pyrrol forms a potassium salt, the imino-hydrogen of the pyrrol group being replaced in the usual way by the metallic atom; and from this salt, by the action of methyl iodide, we obtain the methyl derivative of the iodomethylate (IV.). On distillation with lime, this forms the base nicotyrine (V.)—

(IV.)



(V.)

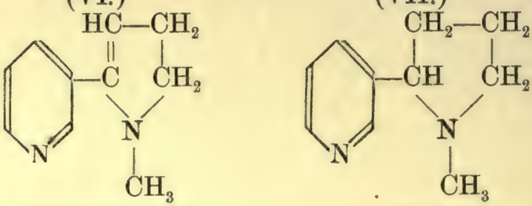


Nicotyrine.

[1] Pictet and Crépieux, *Ber.*, 1895, **28**, 1904.
[2] Pictet, *C. R.*, 1903, **137**, 860.

Now, this body cannot be reduced direct to nicotine, for any agent which attacks the pyrrol nucleus will, at the same time, reduce the pyridine ring. The transformation can be carried out in the following way, however. The nicotyrine (V.) is treated with iodine in alkaline solution, by which means a mono-iodine derivative is produced; it in turn is acted on by tin and hydrochloric acid, whereby it is partially reduced, forming dihydro-nicotyrine (VI.). This substance reacts with bromine to form a perbromide, $C_5H_4N \cdot C_5H_8N \cdot Br_4$, which, by reduction with tin and hydrochloric acid, yields inactive nicotine (VII.). This racemic base can, like coniine, be resolved into its antipodes by means of tartaric acid; so that in this way the synthesis of lævo-nicotine, corresponding to the natural alkaloid, can be accomplished—

(VI.) (VII.)



Dihydro-nicotyrine. Nicotine.

2. *Tropinone, Tropine, and ψ-Tropine.**

Hitherto we have confined our attention to compounds which contain isolated rings of carbon and nitrogen atoms; but with the tropine series we enter a new class in which we shall have to deal with bridged rings analogous to those of the dicyclic terpenes. The first member of the group is tropinone.

This substance was originally prepared by an extremely round-about method;[1] but a new direct synthesis has been devised by Robinson,[2] so that it is unnecessary to describe the older method, which involved nearly twenty stages.

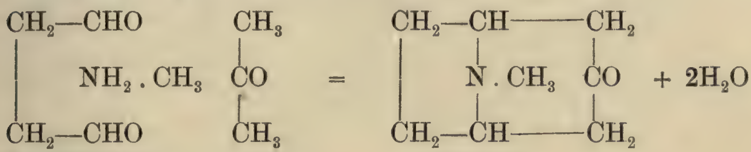
Succindialdehyde (obtained from succindialdoxime and nitrous fumes) was allowed to interact in aqueous solution

* The Greek ψ is used instead of the word "pseudo". Thus ψ-tropine represents pseudo-tropine.

[1] Willstätter, *Annalen*, 1901, **317**, 268; 1903, **326**, 1; *Ber.*, 1901, **34**, 3163; Willstätter and Iglauer, *ibid.*, 1900, **33**, 1170.

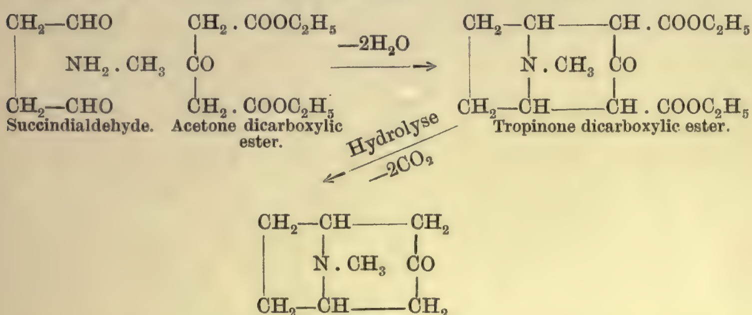
[2] Robinson, *Trans.*, 1917, **111**, 762.

with methylamine and acetone for half an hour, when it was found that tropinone was formed:—



Succindialdehyde. Acetone. Tropinone.

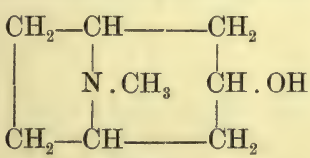
Better yields can be obtained by substituting for acetone the ester or calcium salt of acetone dicarboxylic acid. The intermediate product is a tropinone dicarboxylic acid from which two molecules of carbon dioxide can be split off by acidifying and heating the solution—



Succindialdehyde. Acetone dicarboxylic ester. Tropinone dicarboxylic ester.

Tropinone.

From tropinone, tropine itself can be obtained [1] by the action of zinc dust and concentrated hydriodic acid—

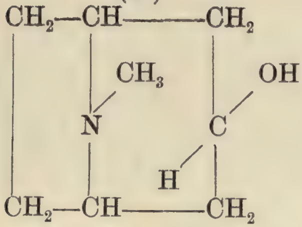


Tropine.

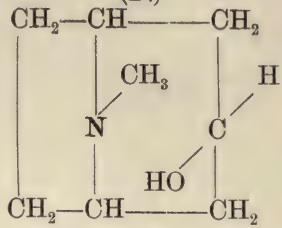
The isomerism of tropine and ψ-tropine may be explained very simply. If the space formula of a compound having the constitution of tropine be built up, it will be found that there are two possibilities: the hydroxyl and the methyl groups may lie on the same side of the ring as in (A), or on opposite sides as in (B)—

[1] Willstätter and Iglauer, *Ber.*, 1900, **33**, 1170.

(A.)



(B.)

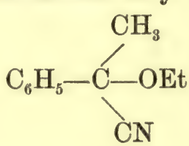


Of the two, tropine is the labile isomer, so that we can convert it at will into ψ-tropine.

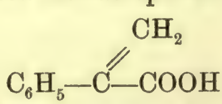
3. *Tropic Acid.*

By the synthesis of tropine we have approached that of another alkaloid, atropine. This substance, when boiled with baryta water, breaks down into tropine and tropic acid. We have thus established the constitution of half the atropine molecule; and in the present section we shall deal with the constitution of the other portion.

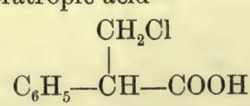
Tropic acid has been synthesized by Ladenburg and Rügheimer.[1] Acetophenone is treated with pentachloride of phosphorus, whereby the oxygen atom is replaced by two chlorine ones, and acetophenone chloride is formed. This is allowed to react with potassium cyanide in alcoholic solution to form the nitrile of atrolactinic ethyl ether—



The nitrile is then hydrolyzed, forming the acid. When this body is boiled with concentrated hydrochloric acid it loses alcohol, and is converted into atropic acid—

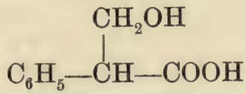


Hydrochloric acid then attaches itself to the double bond, yielding β-hydrochloratropic acid—



[1] Ladenburg and Rügheimer, *Ber.*, 1880, **13**, 376, 2041.

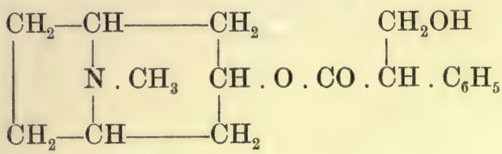
This substance, when boiled with potassium carbonate, exchanges a chlorine atom for a hydroxyl group, and is converted into tropic acid—



Tropic acid.

4. *Atropine.*

The constitutions of the two halves of the atropine molecule have now been established, and the atropine synthesis can be carried out by treating a mixture of tropine and tropic acid with hydrochloric acid gas in the usual way.[1] Atropine, therefore, is the tropine ester of tropic acid, and it must have the constitution shown by the following formula :—



Atropine.

5. *Ecgonine.*

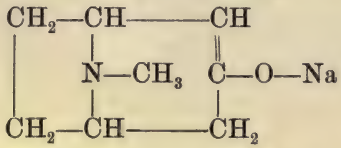
Tropinone forms salts with alkalis, and these, by treatment with carbon dioxide in the usual way, can be converted into the alkali salts of carboxylic acids.[2] In the case of the sodium salt, it is suspended in ether, and carbon dioxide is passed through the liquid at ordinary temperatures; the resulting product is the sodium salt of tropinone carboxylic acid, and when this is reduced with sodium amalgam in a weakly acid solution it yields a mixture of two isomeric bodies having the same composition as ecgonine, $C_8H_{14}NO . COOH$.

The two isomers, however, differ in character. The one has all the properties of ecgonine, except the power of rotating the plane of polarization; it is a true carboxylic acid, forming salts and esters, it also possesses a free hydroxyl group, and can be converted into esters by acids. The second isomer, on the other hand, behaves quite differently. It possesses no free

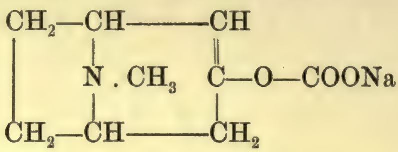
[1] Ladenburg, *Ber.*, 1879, **12**, 941; 1880, **13**, 104.
[2] Willstätter and Bode, *Ber.*, 1900, **33**, 411.

hydroxyl group; nor can it be esterified by the ordinary methods. An explanation of the formation of two such substances is to be found by considering the character of the sodium derivative of tropinone.

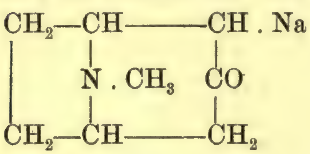
It is well known that the sodium salts of ketonic bodies usually exist in the enolic form, so that we should incline to write the formula of the tropinone sodium salt thus—

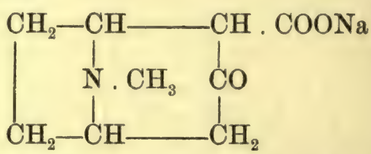


The action of carbon dioxide upon this would produce a sodium salt whose constitution could be written—

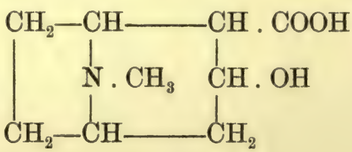


This body forms by far the greater proportion of the reaction mixture, but since the sodium salt of tropinone exists in the keto- as well as in the enol-form, part of the end-product will have the constitution shown below—





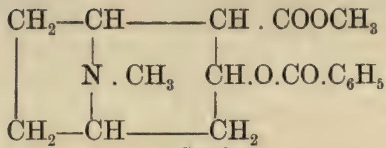
This last substance, on reduction, would give us the alcohol—



which proves to be racemic ecgonine.

6. *Cocaine.*

From ecgonine, cocaine can be prepared by benzoylating the alcohol radicle, and then esterifying the carboxyl group with methyl alcohol—



Cocaine.

E.—The Quinoline Group.

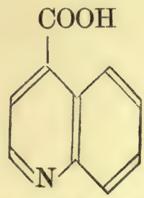
1. *The Constitution of Cinchonine.*

The alkaloid cinchonine has the composition $C_{19}H_{22}ON_2$. The oxygen atom forms part of a hydroxyl group, as is shown by acetylation; and the two nitrogen atoms are tertiary ones.

I. When cinchonine is oxidized by means of chromic acid and sulphuric acid[1] it breaks down into two substances, cinchonic acid and meroquinene, in accordance with the following equation:—

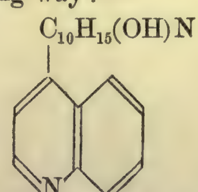
$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 3O = \underset{\text{Cinchonic acid.}}{C_{10}H_7O_2N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

Cinchonic acid has been shown to be a quinoline carboxylic acid of the formula—



so that cinchonine itself must be a γ-quinoline derivative.

For the sake of convenience, we will refer to the two halves of the cinchonine molecule as the "quinoline half" and the "second half". It is obvious that the hydroxyl group which is known to exist in the cinchonine molecule must be situated in the "second half"; for if it were in the "quinoline half" it would appear in cinchonic acid. We may therefore formulate cinchonine in the following way:—

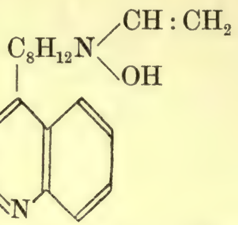


[1] Königs, *Ber.*, 1894, **27**, 1501.

II. Now, when cinchonine is oxidized with potassium permanganate[1] instead of chromic acid, the decomposition products are quite different from those obtained before. The reaction takes the course shown below—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 4O = \underset{\text{Cinchotenine.}}{C_{18}H_{20}O_3N_2} + H.COOH$$

This new oxidation product, cinchotenine, contains the quinoline nucleus (as is shown by its behaviour on further oxidation). It is therefore produced by a decomposition in the "second half" of the molecule. It contains a hydroxyl and a carboxyl group. Cinchonine can take up one molecule of a halogen acid, but cinchotenine has lost this property. Hence the group CH_2 of cinchonine has been split off, leaving the carboxyl group in cinchotenine. We may thus carry our deductions a step further, and write the formula of cinchonine in the following way :—



III. We must now turn to a different reagent. When cinchonine is treated with phosphorus pentachloride and then with alcoholic potash it loses a molecule of water and is converted into cinchene[2]—

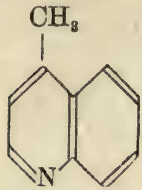
$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} - H_2O = \underset{\text{Cinchene.}}{C_{19}H_{20}N_2}$$

When heated with 25 per cent. phosphoric acid,[3] cinchene takes up two molecules of water and is decomposed into lepidine and meroquinene—

$$\underset{\text{Cinchene.}}{C_{19}H_{20}N_2} + 2H_2O = \underset{\text{Lepidine.}}{C_{10}H_9N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

Lepidine is known to have the formula—

[1] Königs, *Annalen*, 1879, **197**, 374.
[2] Comstock and Königs, *Ber.*, 1884, **17**, 1985.
[3] Königs, *Ber.*, 1890, **23**, 2677 ; 1894, **27**, 900.



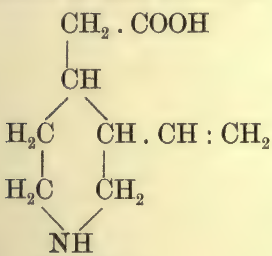
IV. Meroquinene is the next substance whose decompositions must be examined. When it is oxidized with an ice-cold mixture of sulphuric acid and potassium permanganate it gives cincholoiponic acid[1]—

$$\underset{\text{Meroquinene.}}{C_9H_{15}O_2N} + 4O = \underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + H.COOH$$

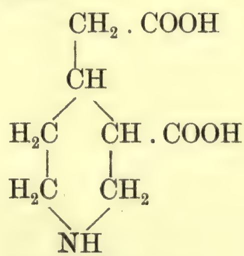
This, by the action of aqueous permanganate, is converted into loiponic acid[2]—

$$\underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + O_2 = \underset{\text{Loiponic acid.}}{C_7H_{11}O_4N} + H.COOH$$

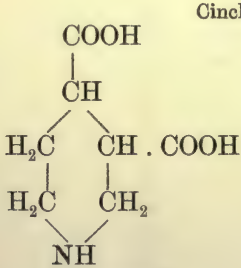
Loiponic acid is an unstable form of hexahydrocinchomeronic acid, for on heating with caustic potash it is converted into that substance by isomeric change. By assuming the *structure* of loiponic acid to be the same as that of hexahydrocinchomeronic acid (the *configurations* of the two being different), we can work back step by step to meroquinene, whose formula must therefore be that shown in the series below—



Meroquinene.



Cincholoiponic acid.



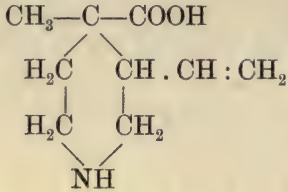
Loiponic acid.

[1] Königs, *Ber.*, 1895, **28**, 1986, 3150.

[2] Skraup, *Monatsh.*, 1896, **17**, 377 ; Königs, *Ber.*, 1897, **30**, 1329.

The position of the $—CH_2 . COOH$ group of meroquinene is uncertain.

The formula above is due to Königs, but the alternative put forward by Miller and Rohde[1]—

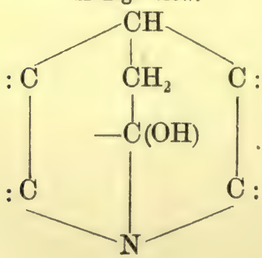


has probably as much to recommend it.

Of the ten carbon atoms of the "second half" we have thus established the mode of linkage of eight: five in a piperidine ring, two in a vinyl group, and one in a methyl or methylene group. The ninth carbon atom of the "second half" must be utilized in joining the two halves together. Thus we have only to determine the position of the tenth carbon atom of the "second half".

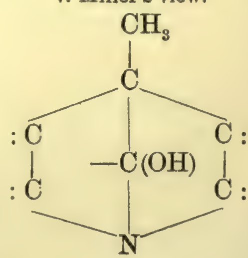
V. It will be remembered that the two nitrogen atoms of cinchonine are tertiary; but it has been shown that the nitrogen atom of meroquinene is a secondary one. This has been established by the usual reactions of the imido group, and agrees with the constitution which we have ascribed to meroquinene in the previous paragraph. This peculiar behaviour of the nitrogen atom can best be explained by the assumption that in the "second half" of cinchonine we have a nucleus of either of the types (I.) or (II.)—

Königs' view.



(I.)

v. Miller's view.

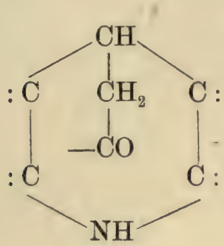


(II.)

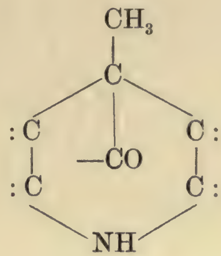
When such a nucleus as (I.) is heated with dilute acids it

[1] Miller and Rohde, *Ber.*, 1895, **28**, 1060.

will undergo intramolecular change into an imido-ketone in the way expressed by the formula (I.*a*) below. If the type (II.) be chosen itstead of (I.) the analogous substance (II.*a*) would be produced in the same way—



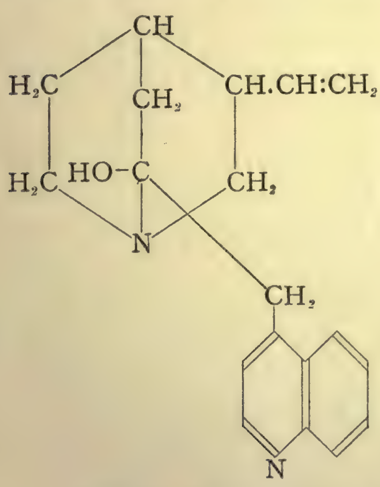
(I.*a*)

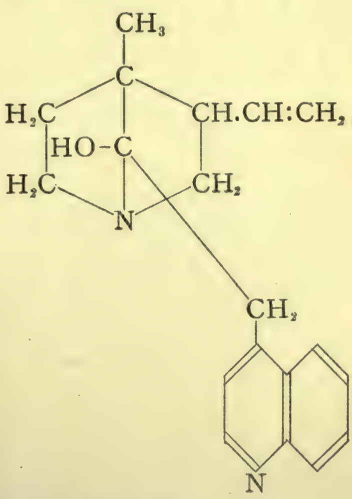


(II.*a*)

Such a change actually occurs when cinchonine is heated with dilute acetic acid; an imido-ketone results, which, on account of its poisonous properties, is named "*cinchotoxine*".[1] Thus it is apparent that across the piperidine ring there is a bridge of one carbon atom, and this accounts for the missing tenth carbon atom in the "second half" of cinchonine.

From the foregoing evidence, cinchonine would be represented by either of the two formulæ below—





[1] Miller and Rohde, *Ber.*, 1894, **27**, 1187, 1279; 1895, **28**, 1056.

2. *The Constitution of Quinine.*

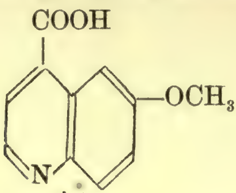
Knowing the constitution of cinchonine, we can easily prove that of quinine.

I. Quinine differs from cinchonine by one carbon, one oxygen, and two hydrogen atoms—

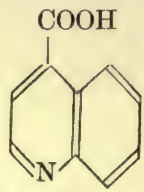
$$\underset{\text{Quinine.}}{C_{20}H_{24}O_2N_2} - \underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} = CH_2O$$

This points to quinine being a methoxy derivative of cinchonine, if we bear in mind the similarity in character between the two substances.

II. When oxidized with sulphuric and chromic acids,[1] quinine gives the acid (A); whereas it will be remembered that cinchonine gave cinchonic acid (B). Meroquinene is one of the oxidation products in both cases—

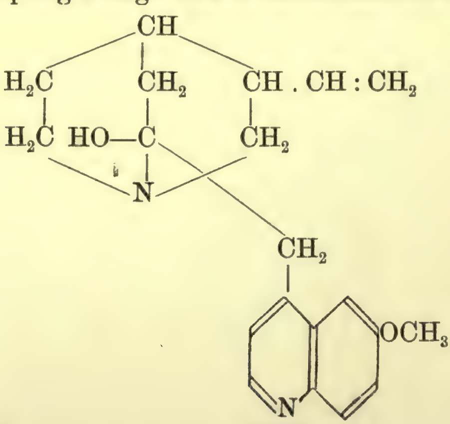


(A.)



(B.)

III. This proves the presence and position of the methoxyl group in quinine; and since in its reactions quinine forms an exceedingly close analogue to cinchonine, we are justified in concluding that it is a methoxy-cinchonine of the following constitution (accepting Königs' view of the structure of cinchonine):—



Quinine.

[1] Skraup, *Monatsh.*, 1881, **2**, 591; 1883, **4**, 695; 1891, **12**, 1106; 1895, **16**, 2684.

3. *Cinchonidine and Conchinine.*

Cinchonine has three asymmetric carbon atoms in its molecule, and therefore it may occur in several stereoisomeric forms. Cinchonidine is supposed to be one of these; while conchinine is a stereoisomer of quinine.

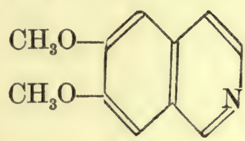
F.—The Isoquinoline Group.

1. *The Constitution of Papaverine.*

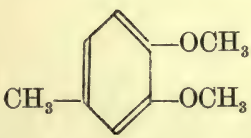
The constitution of papaverine is a much simpler question than that with which we have just dealt in the case of cinchonine. There are six steps in the argument.[1]

I. In the first place, the formula of papaverine is $C_{20}H_{21}O_4N$; it contains four methoxyl groups, which can be hydrolyzed, yielding the substance papaveroline, $C_{16}H_9N(OH)_4$. This accounts for all the oxygen atoms.

II. On fusion with alkali, papaverine breaks down into two nuclei, one of which contains nitrogen, while the other nucleus is nitrogen-free. The first was proved to be a dimethoxyquinoline of the constitution—



while the second decomposition product was dimethylhomocatechol—



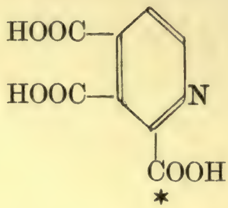
III. The fact that these two groups are *directly* united to one another follows from the composition of the two decomposition products—

$$\underset{\text{Papaverine.}}{H_2 + C_{20}H_{21}O_4N} = \underset{\text{Dimethoxyquinoline.}}{C_{11}H_{11}O_2N} + \underset{\text{Dimethoxyhomocatechol.}}{C_9H_{12}O_2}$$

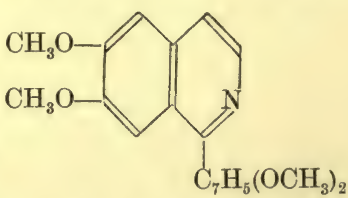
[1] Goldschmiedt, *Monatsh.*, 1883, **4**, 704; 1885, **6**, 372, 667, 954; 1886, **7**, 485; 1887, **8**, 510; 1888, **9**, 42, 327, 349, 679, 762, 778; 1889, **10**, 673, 692.

IV. We must now examine the question of the manner in which the two nuclei are united. Since papaverine contains four methoxy groups, and each of the decomposition products contains two, it is obvious that during the decomposition no methoxy group is destroyed. Now, if the link between the two nuclei had been an oxygen atom, *i.e.* if papaverine had contained the grouping R—O—CH_2—O—R, then in the breakdown of the molecule one -O . CH_2 . O- group would have been destroyed. We may therefore exclude the idea of joining the two nuclei through an oxygen atom, and must assume that they are directly united, carbon to carbon.

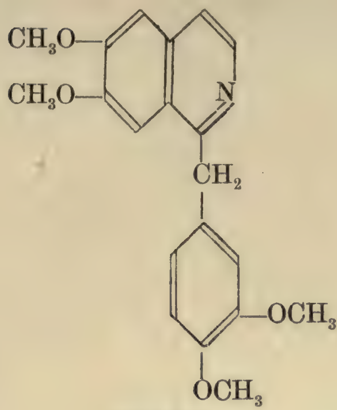
V. Our next problem is to find which carbon atom of the isoquinoline ring is joined to the other nucleus. When we oxidize papaverine with potassium permanganate, we obtain *a*-carbocinchomeronic acid—



Hence we deduce that the side-chain (second nucleus) was attached at the point now occupied by the carboxyl group, which is marked with an asterisk. Papaverine is therefore—



VI. We have now to settle the constitution of the group —$C_7H_5(OCH_3)_2$. This must be the dimethoxy-homocatechol radicle, which has the same composition. We have only to decide whether the two nuclei are joined ring to ring or by the intermediation of the side-chain of the dimethoxy-homocatechol. Without going into details, it may be said that all the evidence points to the union being made through the side-chain. The constitution of papaverine is therefore—

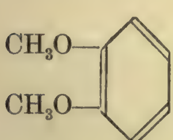


Papaverine.

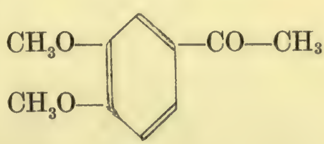
2. *The Synthesis of Papaverine.*

The synthesis of papaverine has recently been carried out by Pictet and Gams.[1] The reactions may be grouped in five stages.

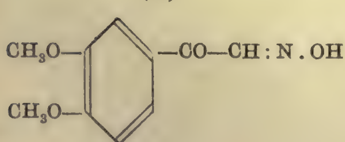
I. The first step in the process is the synthesis of amino-aceto-veratrone. For this purpose veratrol (I.) is treated with acetyl chloride in presence of aluminium chloride, whereby aceto-veratrone (II.) is formed. When this is treated with sodium ethylate and amyl nitrate, it yields the isonitroso-derivative (III.), which can then be reduced by tin chloride and hydrochloric acid to the hydrochloride of amino-aceto-veratrone (IV.)—



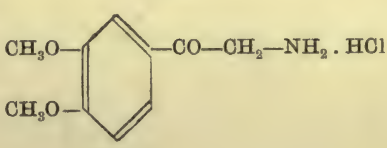
(I.)



(II.)



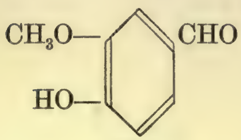
(III.)



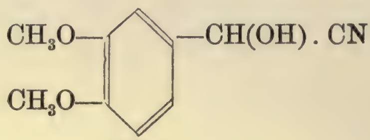
(IV.)

[1] Pictet and Gams, *C. R.*, 1909, **149**, 210.

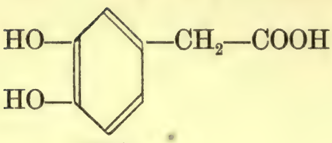
II. We must now turn to the synthesis of homoveratroyl chloride. Vanillin (V.) is methylated and then treated with hydrocyanic acid, giving dimethoxy-mandelic nitrile (VI.). When this is boiled with hydriodic acid three processes take place simultaneously; reduction, hydrolysis, and the splitting off of methyl radicals. We thus obtain homoprotocatechuic acid (VII.) and by methylation of the hydroxyl groups followed by the action of phosphorus pentachloride the chloride of homoveratric acid is formed (VIII.)—



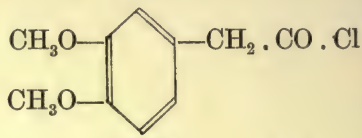
(V.)



(VI.)

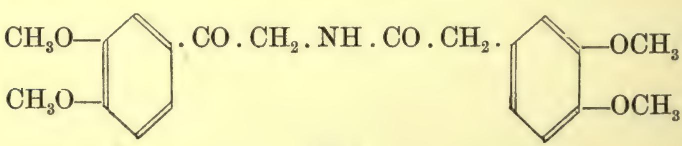


(VII.)



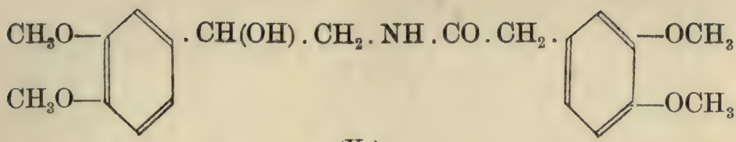
(VIII.)

III. If we now allow the amino-aceto-veratrone hydrochloride obtained in Stage **I.** to interact with the homoveratric chloride of Stage **II.** in presence of alkali, we obtain homoveratroyl-amino-aceto-veratrone (IX.)—



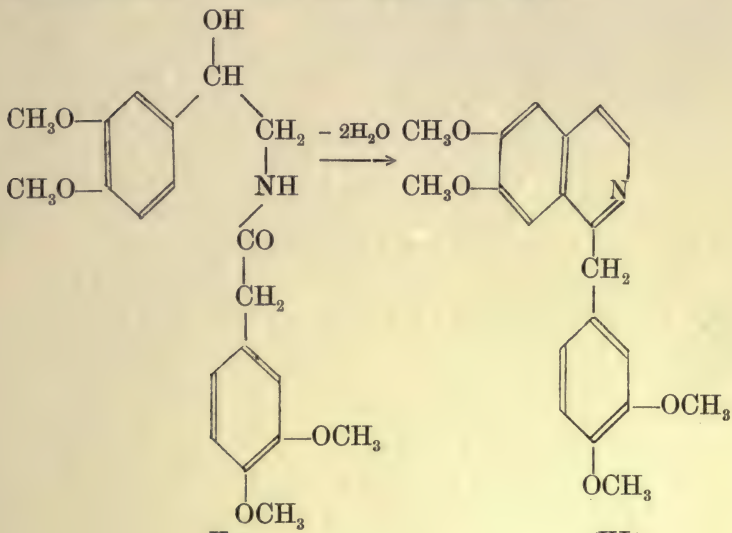
(IX.)

IV. An inspection of the formula (IX.) will show that though the substance contains two carbonyl groups, one of these is a true carbonyl while the other is a radicle which originally formed part of a carboxyl group. When the substance is reduced with sodium amalgam in neutral alcoholic solution, the true carbonyl is reduced, while the acidic carbonyl remains unaffected. The product is homoveratroyl-hydroxy-homoveratrylamine (X.)—



(X.)

V. When this substance (X.) is treated with phosphorus pentoxide in boiling xylene solution, it loses two molecules of water and is converted into papaverine (XI.)—

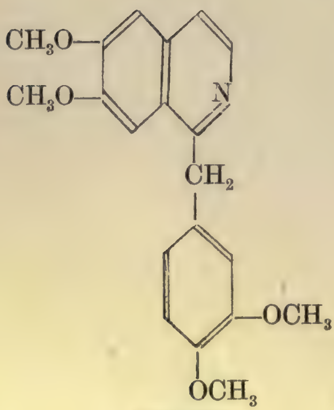


(X.) (XI.)

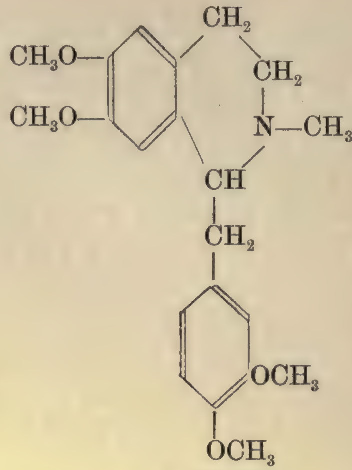
3. *The Synthesis of Laudanosine.*

In the preceding section we have seen how the synthesis of papaverine may be accomplished, and we are now in a position to consider the question of a closely related alkaloid, laudanosine. This body is very simply produced from papaverine. Pictet and Athanasescu[1] showed that if we form the chloro-methyl derivative of papaverine and then reduce this with tin and hydrochloric acid we obtain methyl-tetrahydropapaverine. This synthetic substance is of course racemic; and from it the dextro-antipode was obtained in the usual way by making the quinic acid salt of the alkaloid and fractionally crystallizing it. The substance thus obtained was found to be identical with natural laudanosine—

[1] Pictet and Athanasescu, *Ber.*, 1900, **33**, 2346.



Papaverine.



Laudanosine.

Pictet and Finkelstein[1] have recently carried out the complete synthesis of laudanosine, but as the method is very similar to that which we have already described in the case of papaverine we need not enter into it here.

4. *Opianic Acid.*

Though opianic acid itself is not an alkaloid, we must take up its constitution at this point owing to its relation with narcotine, with which we shall deal later.

I. When narcotine is hydrolyzed with barium hydrate or sulphuric acid,[2] it decomposes into opianic acid and hydrocotarnine—

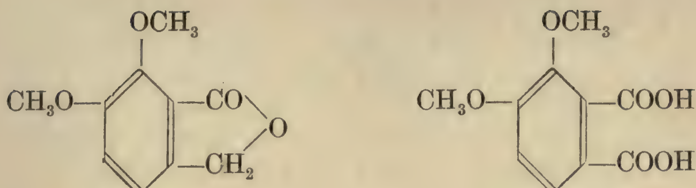
$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N}$$

II. Opianic acid is a monobasic acid, and therefore we may write its formula $C_9H_9O_3 . COOH$.

III. When heated with hydriodic acid, two methyl groups are split off from opianic acid.[3] It therefore contains two methoxy groups, and may be written thus, $(CH_3O)_2 . C_7H_3O . COOH$.

IV. When heated with potash[4] it gives (by reduction) meconine, and (by oxidation) hemipinic acid—

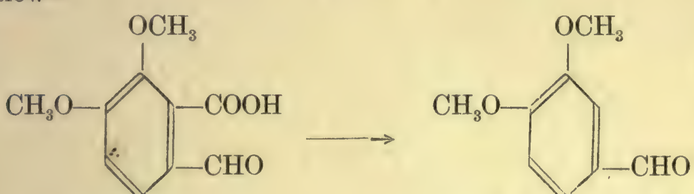
[1] Pictet and Finkelstein, *Ber.*, 1909, **42**, 1979; *C. R.*, 1909, **148**, 925.
[2] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 583.
[3] Matthiessen and Foster, *Annalen Suppl.*, I., 333; II., 378; V., 333.
[4] *Ibid.*, I., 332; II., 381.



Meconine. Hemipinic acid.

This last reaction is parallel to the formation of benzyl alcohol and benzoic acid by the action of potash upon benzaldehyde, so we must conclude that opianic acid contains an aldehydic group; and from the constitution of hemipinic acid it is obvious that this aldehyde radicle must be next the carboxyl group of opianic acid.

V. The final proof of the presence of an aldehyde group in opianic acid is furnished by the behaviour of its sodium salt when distilled with soda-lime.[1] Carbon dioxide is split off in the usual way, and the methyl ether of vanillin is left. The formula of opianic acid must therefore be that which is shown below—



Opianic acid. Methyl ether of vanillin.

5. *The Constitution of Cotarnine.*

The next stage in the proof of the narcotine constitution is reached through the constitution of cotarnine. This substance[2] is obtained along with opianic acid when narcotine is treated with oxidizing agents—

$$C_{22}H_{23}O_7N + O + H_2O = C_{10}H_{10}O_5 + C_{12}H_{15}O_4N$$

Narcotine. Opianic acid. Cotarnine.

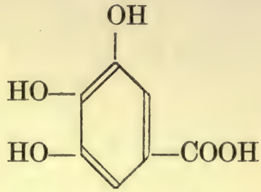
I. Cotarnine reacts with two molecules of methyl iodide, thus proving that it is a secondary base. The reaction product is called cotarnomethine methyl iodide,[3] and has the composition $C_{11}H_{11}O_4N(CH_3)_3I$.

[1] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 583.
[2] Wöhler, *Annalen*, 1844, **50**, 1.
[3] Roser, *Annalen*, 1888, **249**, 157.

II. By heating this body with caustic soda, trimethylamine is split off,[1] and cotarnone, $C_{11}H_{10}O_4$, remains. This proves to be an aldehyde, so that its formula can be written $C_{10}H_9O_3 . CHO$.

III. When cotarnone is oxidized with potassium permanganate [2] it gives a lactone, cotarnolactone, $C_{11}H_{10}O_6$, from which, on further oxidation, cotarnic acid, $C_{10}H_8O_7$, is obtained.

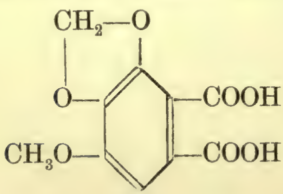
IV. By the usual reactions it is found that cotarnic acid [3] is dibasic, contains a methoxyl radicle, and has its carboxyl groups in the ortho-position to one another, as is shown by the ease with which it forms an anhydride. When heated with phosphorus and hydriodic acid to about 160° C. it yields gallic acid—



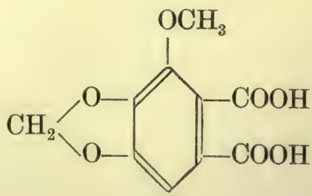
V. Now, gallic acid differs from cotarnic acid by the group $C_3H_2O_2$—

$$\begin{array}{ccccccc} C_{10}H_8O_7 & - & C_7H_6O_5 & = & CH_2 & + & CO_2 + C \\ \text{Cotarnic acid.} & & \text{Gallic acid.} & & \text{From methoxy group.} & & \end{array}$$

Part of this we can account for by the loss of carbon dioxide from a carboxyl group, since cotarnic acid is dibasic, while gallic acid is monobasic. We have thus one carbon atom left unaccounted for. This must be derived from the methylene group of a methylene ether. We are in this way led to formulate cotarnic acid as a methyl-methylene-gallic-carboxylic acid, $C_6H(OCH_3)(CH_2O_2)(COOH)_2$. For such a substance there are only two possible formulæ—



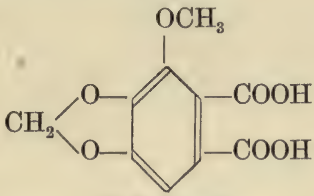
(I.)



(II.)

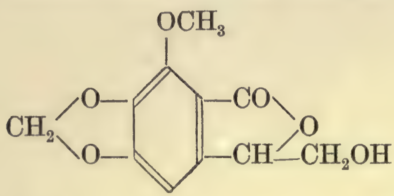
[1] Roser, *Annalen*, 1888, **249**, 141.
[2] *Ibid.*, 163.
[3] *Ibid.*, 163; 1899, **254**, 341.

Without going into details,[1] we may say that the general behaviour of the substance is best represented by (II.). Cotarnic acid therefore has the constitution—

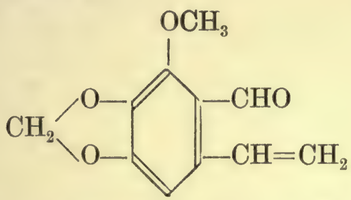


Cotarnic acid.

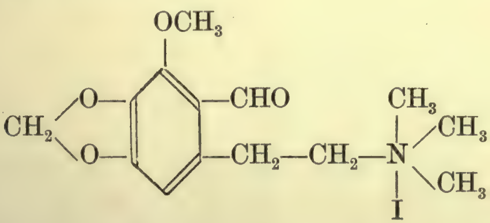
VI. Cotarnolactone must therefore have the formula—



and cotarnone must be—

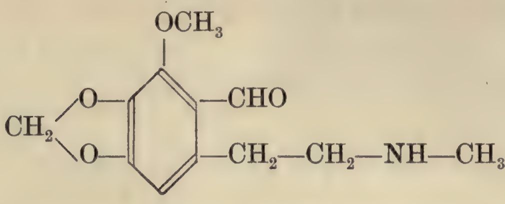


VII. But cotarnone was obtained from cotarnomethine methyl iodide and soda, whence cotarnomethine methyl iodide must have the structure—

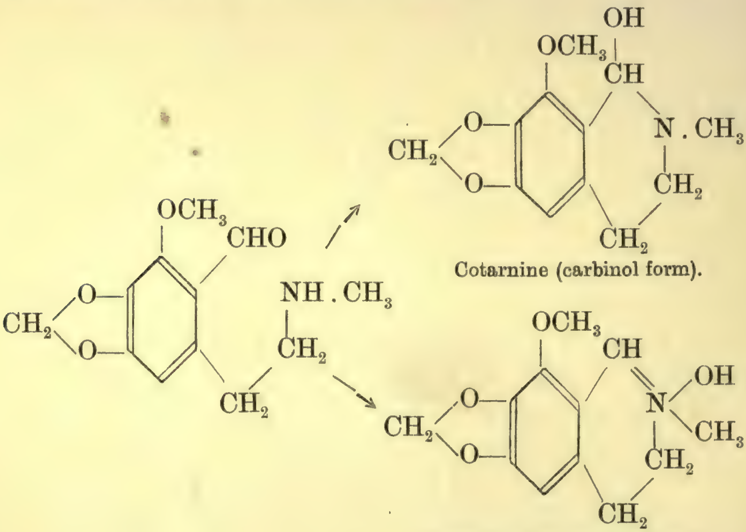


VIII. Hence cotarnine should have the following constitution; since cotarnomethine methyl iodide is obtained from it by the action of two molecules of methyl iodide—

[1] Freund and Becker, *Ber.*, 1903, **36**, 1521.



IX. This formula, however, fails to explain the formation of a pyridine derivative, apophyllenic acid, when cotarnine is oxidized with nitric acid;[1] and to account for this we must assume that the free aldehydic group has disappeared in the course of some intramolecular ring-formation, which simultaneously brings into existence a pyridine chain within the molecule of cotarnine. This change we may represent in two ways, as shown in the formulæ below—

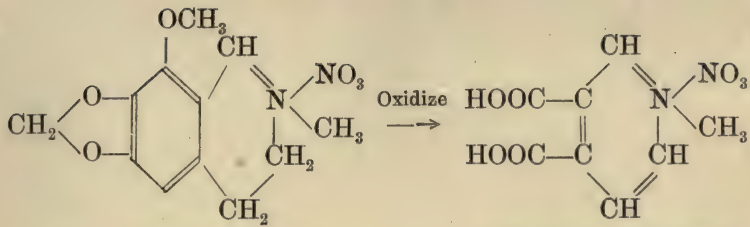


Cotarnine (carbinol form).

Cotarnine (ammonium form).

It is generally agreed that the salts of cotarnine are best represented as derivatives of the ammonium form; for instance, the production of apophyllenic acid can be made clear on this assumption—

[1] Wöhler, *Annalen*, 1844, **50**, 24.



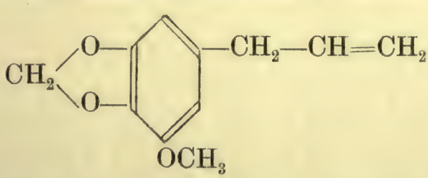
Cotarnine nitrate. Apophyllenic acid derivative.

With regard to the free base, however, the spectroscopic investigations of Dobbie, Lauder, and Tinkler[1] have shown that the structure varies with the solvent in which the substance is dissolved. In ether or chloroform the carbinol form is present; but the addition of alcohol to the solution brings into existence the ammonium form; in pure alcoholic solution no less than 25 per cent. of the substance is present as ammonium base.

6. *The Synthesis of Cotarnine.*

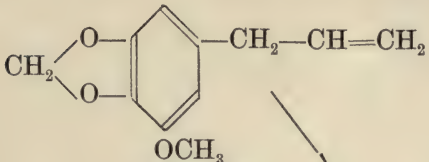
In the last section we dealt with the constitution of cotarnine, and we must now take up the synthesis of this substance. Synthetic cotarnine has been prepared by Salway;[2] but as the constitution of one of his intermediate products is left doubtful in the synthesis, it is not possible to establish the cotarnine structure from his work. In the light of the facts given in the last section, however, we can deduce the formulæ of the intermediate compounds.

I. The first stage in the process is the synthesis of β-3-methoxy-4 : 5-methylenedioxy-phenyl-propionic acid. Salway took as his starting-point the substance myristicin—

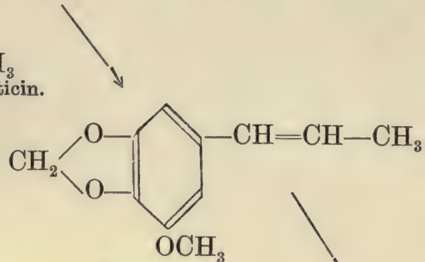


which he obtained from oil of nutmeg. This was heated with alcoholic potash to convert it into iso-myristicin; and the latter was then oxidized to myristicin aldehyde by means of potassium permanganate—

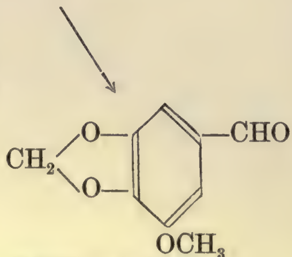
[1] Dobbie, Lauder, and Tinkler, *Trans. Chem. Soc.*, 1903, **83**, 598.
[2] Salway, *Trans. Chem. Soc.*, 1910, **97**, 1208.



Myristicin.

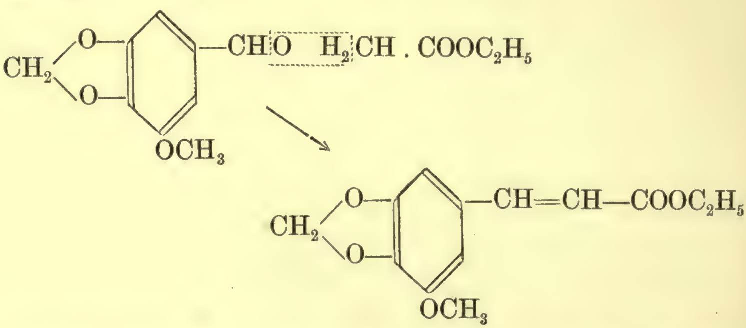


Isomyristicin.

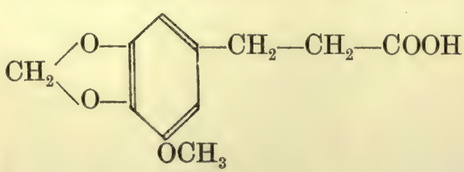


Myristicin aldehyde.

The aldehyde was then condensed with ethyl acetate by means of sodium, and the resulting ester was hydrolyzed with alcoholic potash—

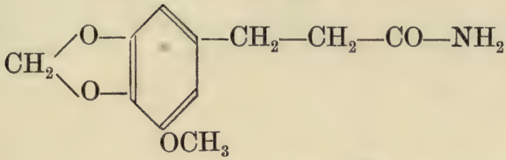


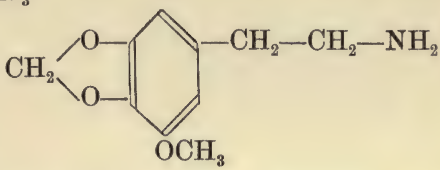
The substituted cinnamic acid thus produced was reduced with sodium amalgam, and in this way the required β-3-methoxy-4 : 5-methylenedioxy-phenyl-propionic acid was obtained.



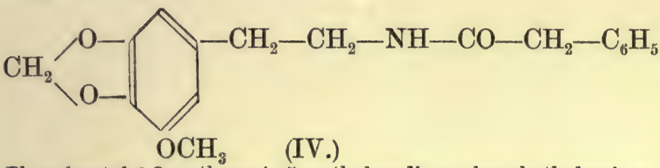
(I.)

II. The second stage ends in the production of phenylacetyl-β-3-methoxy-4 : 5-methylenedioxy-phenyl-ethylamine. The acid (I.) was converted into the amide (II.) in the usual way, and this in turn was changed into the corresponding amine (III.) by Hofmann's reaction—

(II.) 

(III.) 

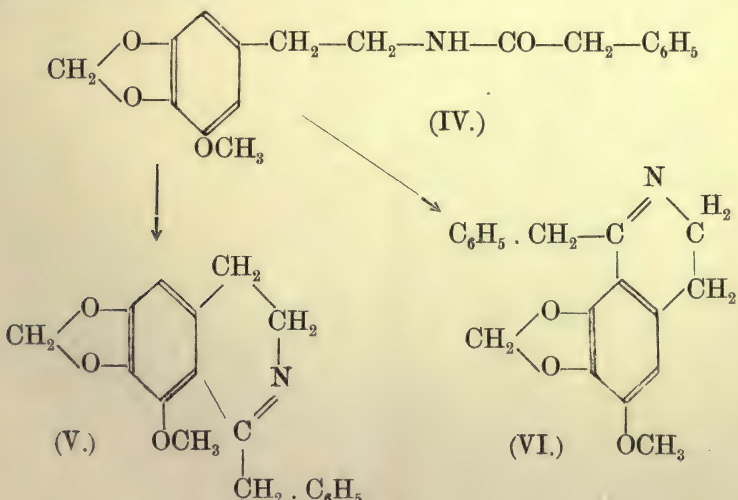
The phenylacetyl derivative (IV.) was then prepared by the ordinary method—



(IV.)

Phenylacetyl-β-3-methoxy-4 : 5-methylenedioxy-phenyl-ethylamine.

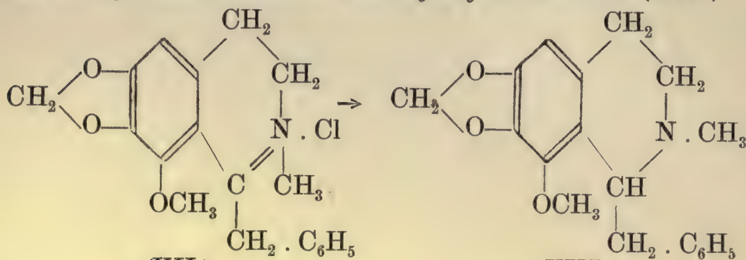
III. This phenylacetyl derivative was condensed by heating it with phosphoric oxide in presence of xylene; and in this way a mixture of two isomeric dihydro-isoquinoline derivatives was produced (V. and VI.).



(IV.)

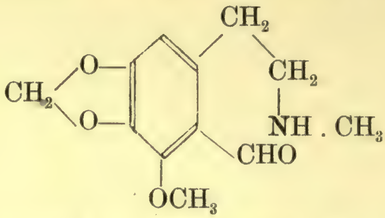
(V.) (VI.)

IV. The substance (V.) is 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro-isoquinoline. To convert it into cotarnine, it is necessary in the first instance to form its metho-chloride (VII.), which is then reduced by means of tin and hydrochloric acid to 1-benzyl-hydrocotarnine (VIII.).



(VII.) (VIII.)

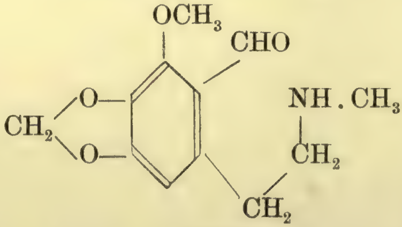
Finally, oxidation with manganese dioxide in presence of sulphuric acid converted the benzyl derivative into cotarnine—



It will be noticed that the substance (VI.), if treated in the same way as (V.), would give rise to an iso-cotarnine; and if the cotarnine constitution were unknown, this synthesis would throw no light upon the relative positions of the methoxy group and the pyridine ring.

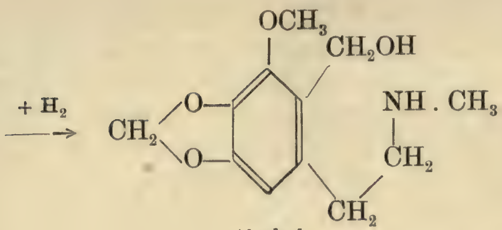
7. *The Synthesis of Hydrocotarnine.*

On reduction, cotarnine is converted into hydrocotarnine,[1] which is formed in the manner indicated by the formulæ below—

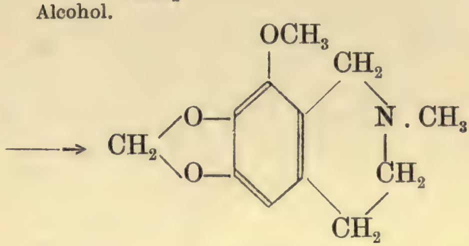


Cotarnine.

[1] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 577; Bandow and Wolffenstein, *Ber.*, 1898, **31**, 1577.



Alcohol.



Hydrocotarnine.

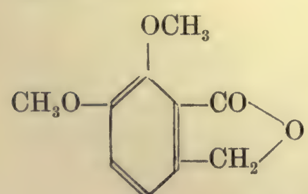
8. *The Constitution of Narcotine.*

We have now in the course of the previous sections amassed the material which we require in our consideration of the narcotine formula ; and we may next proceed to deal with the question.

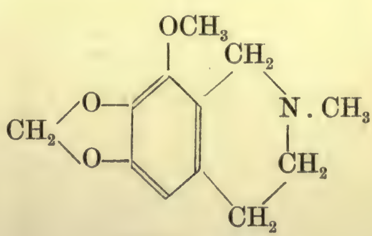
Narcotine contains no carboxyl or hydroxyl radicle. It is made up of one hydrocotarnine nucleus and one opianic acid nucleus, the latter being in the form of the lactone, meconine. This is shown by the action of reducing agents upon narcotine—

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2 = \underset{\text{Meconine.}}{C_{10}H_{10}O_4} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N}$$

We must now consider the mode of linkage of these two nuclei. When we examine the formulæ of meconine and hydrocotarnine—

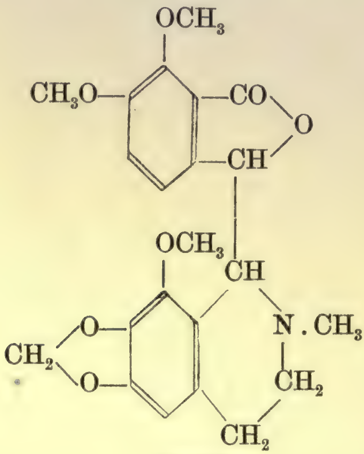


Meconine.



Hydrocotarnine.

it is obvious that the linking does not take place through an oxygen atom, as all of these are fully occupied. It must, therefore, occur by the junction of two carbon atoms, each of which loses a hydrogen atom in the union. The pair of atoms which are most likely to be concerned in the linkage are those which give rise to the aldehyde groups of opianic acid and cotarnine, so that the formula of narcotine would be written—



Narcotine.

9. *The Syntheses of Gnoscopine and Narcotine.*

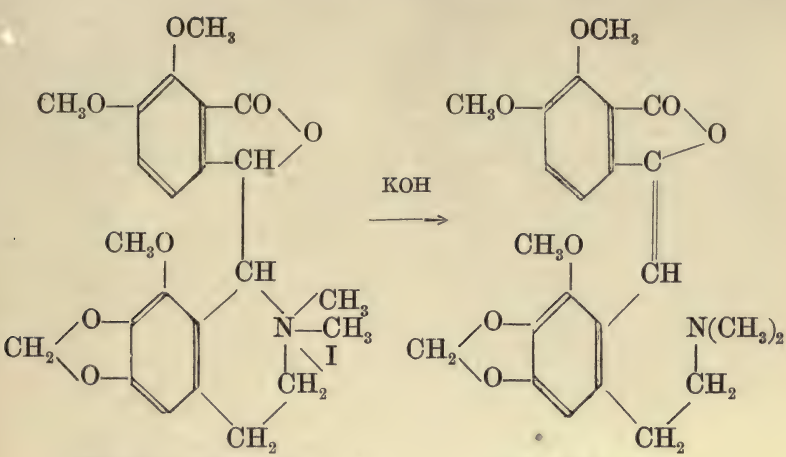
Perkin and Robinson [1] showed that when cotarnine and meconine are boiled in alcoholic solution in presence of potassium carbonate the substance produced is identical with the alkaloid gnoscopine; and by fractionally crystallizing the *d*-bromocamphorsulphonate of the base [2] they were able to isolate the dextro and lævo forms of narcotine, gnoscopine being the racemic variety. The lævo-narcotine thus obtained was identical with the natural alkaloid.

10. *The Synthesis of Narceïne.*

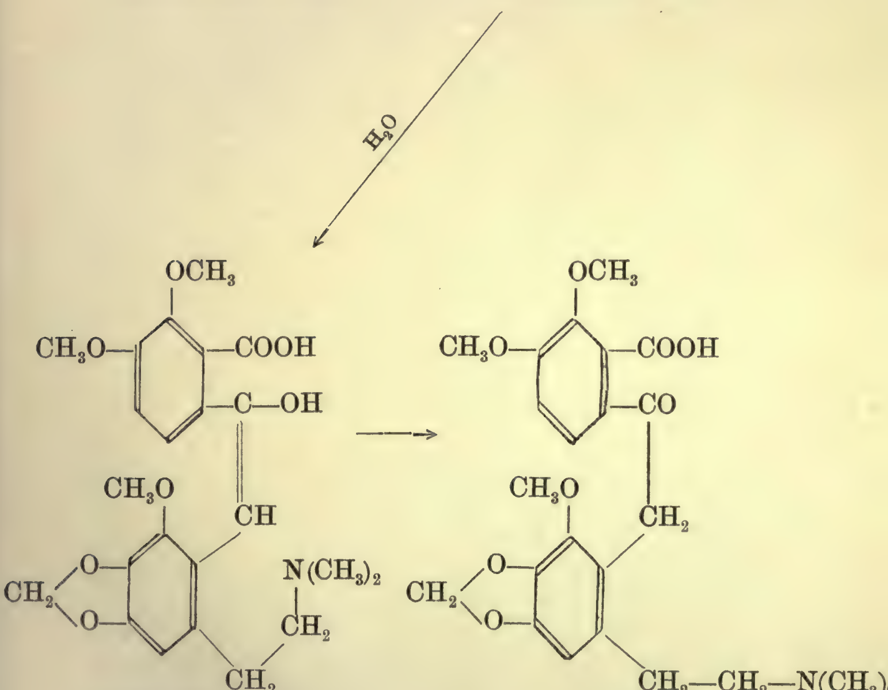
When the methyl iodide addition product of narcotine is treated with alkalis, it is converted into a substance narceïne, which was first called pseudo-narceïne.[3] The course of the reaction may be formulated in the following way:—

[1] Perkin and Robinson, *Proc. Chem. Soc.*, 1910, **26**, 46. [2] *Ibid.*, 131.

[3] Roser, *Annalen*, 1888, **247**, 167; 1889, **254**, 357; Freund and Frankforter, *ibid.*, 1893, **277**, 31.



Narcotine methyl iodide. Intermediate product.



Intermediate product. Narceïne.

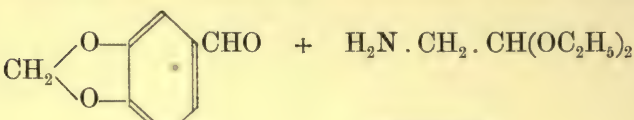
11. *The Synthesis of Hydrastinine.*

This substance, which occurs among the decomposition products of the alkaloid hydrastine, has been synthesized by Fritsch;[1] and as a knowledge of its constitution may help us in our consideration of the hydrastine formula, we may give a brief account of Fritsch's work before dealing with the natural alkaloid.

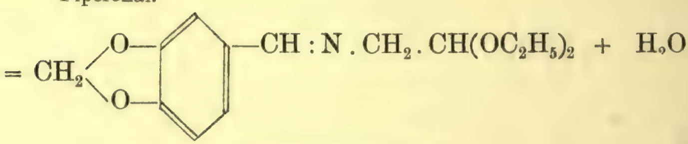
When chloracetal is treated with ammonia, it yields the substance acetalamine, which has the formula—

$$NH_2 . CH_2 . CH(OC_2H_5)_2$$

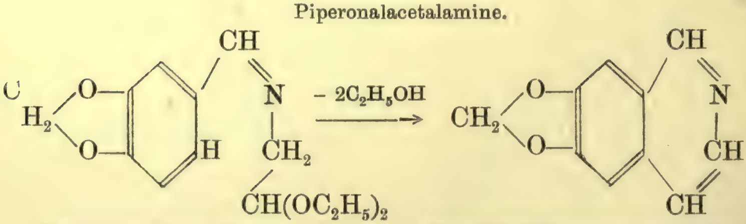
This substance can be made to condense with aromatic aldehydes; and when the products thus obtained are treated with sulphuric acid, alcohol is split off and isoquinoline derivatives are formed. If we apply this reaction to the case of piperonal, we shall have the following series of reactions:—



Piperonal. Acetalamine.



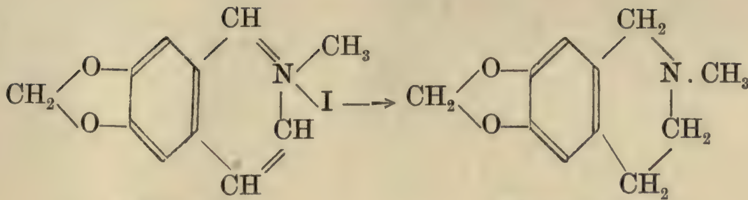
Piperonalacetalamine.



Piperonalacetalamine. Methylenedihydroxyisoquinoline.

When the methyl iodide addition product of this body is reduced by means of tin and hydrochloric acid, it gives the substance hydrohydrastinine—

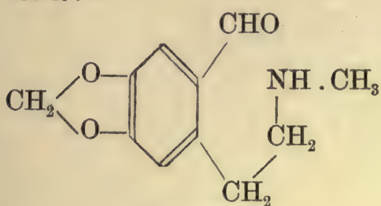
[1] Fritsch, *Annalen*, 1895, **286**, 18.



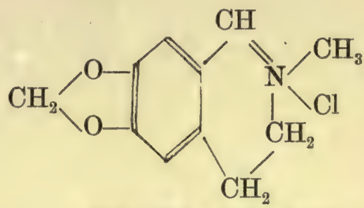
Iodomethylate. Hydrohydrastinine.

This last substance Freund[1] has converted into hydrastinine by oxidizing it with potassium bichromate and sulphuric acid.

Now, from the fact that the behaviour of hydrastinine, on reduction and salt formation, closely resembles that of cotarnine, we are enabled to put forward the following structural formula for it:—



Hydrastinine.



Hydrastinine hydrochloride.

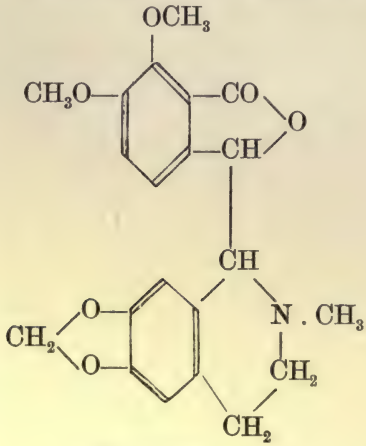
This formula explains why hydrastinine behaves as an aldehyde, why it forms a ring-compound in presence of acids, why its salts contain one molecule of water less than the free base, why it yields apophyllenic acid on oxidation, and many other properties which the substance possesses. A comparison of their formulæ will show that cotarnine is a methoxylated hydrastinine.

12. *The Constitution of Hydrastine.*

Hydrastine contains one methoxyl group less than narcotine, but in all other respects it resembles that compound. Now, on oxidation with dilute nitric acid, hydrastine breaks down into hydrastinine and opianic acid just as narcotine breaks down into cotarnine and opianic acid. But, as was shown in the preceding section, cotarnine is methoxy-hydrastinine, so that we may conclude that if we eliminate the methoxy group from narcotine we shall have hydrastine. This

[1] Freund, *Ber.*, 1887, **20**, 2403.

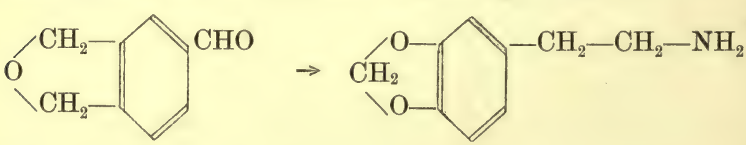
actually proves to be the case; so that we may write the formula of hydrastine by simply taking that of narcotine and replacing the methoxyl radicle of the cotarnine half by a hydrogen atom. Hydrastine would therefore be—



Hydrastine.

13. *The Synthesis of Berberine.*

Piperonal (I.) forms the starting-point of this series of reactions. When it is condensed with nitromethane in presence of sodium methylate, it produces piperonylidene-nitromethane from which in turn homopiperonaldoxime and homopiperonylamine (II.) are obtained by reduction.[1]

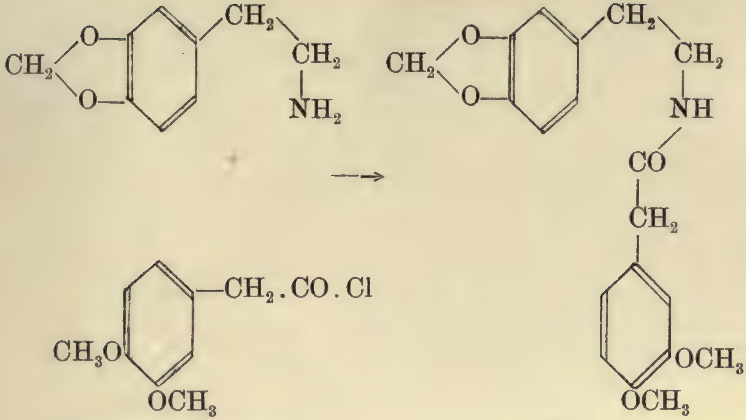


(I.) (II.)

Homoveratroyl chloride (the preparation of which has already been described[2]) is now allowed to act upon the amine yielding a condensation product (III.), which loses one molecule of water when heated with phosphorus pentoxide in xylene solution forming (IV.)—

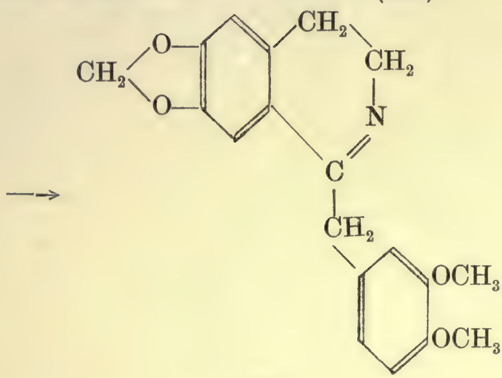
[1] Bouveault and Wahl, *Compt. rend.*, 1902, **135**, 41; Medinger, *Monatsh.*, 1906, **27**, 237.

[2] See p. 146.



Homoveratroyl chloride.

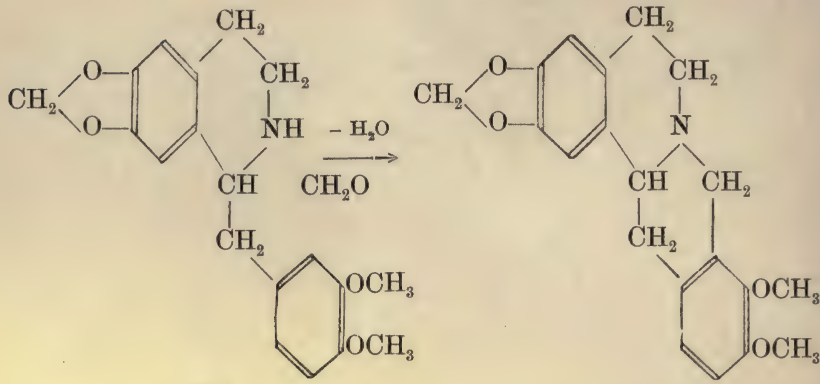
(III.)



(IV.)

When the isoquinoline derivative (IV.) is reduced with tin and hydrochloric acid, it yields veratroyl-norhydrohydrastinine (V.). Condensation of the hydrochloride of this with methylal results in the entry of an extra carbon atom into the molecule, with the formation of a new six-membered ring. This produces tetrahydroberberine;[1] from which berberine itself is obtained by oxidation.[2]

[1] Pictet and Gams, *Compt. rend.*, 1911, **153**, 386; *Ber.*, 1911, **44**, 2480.
[2] Hlasiwetz and Gilm, *Annalen Supp.*, 1863, **2**, 191.



(V.)

Tetrahydroberberine.

The true constitution of berberine is not yet agreed upon; as there are several ways in which hydrogen might be removed from tetrahydroberberine.

G.—The Purine * Group.

1. *The Synthesis of Uric Acid.*

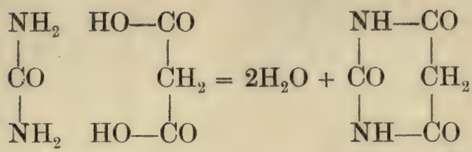
The problem of the constitutions of the purine derivatives has proved one of the most complicated chapters in the recent history of organic chemistry; so complicated is it that we cannot devote space to any historical treatment of the matter, but must confine ourselves as closely as possible to the actual proofs of the constitutions of some of the purine series.

The most important member of the group is uric acid. This substance [1] has been synthesized in a variety of ways; but for the most part the syntheses throw no very clear light upon the constitution of the body. We may describe very briefly two of these synthetic methods of preparing uric acid, the first being due to Emil Fischer and the second to W. Traube.

When malonic acid is treated with urea, it yields a cyclic ureide, malonyl-urea or barbituric acid—

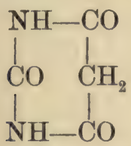
* This, like many other chemical terms, is what Lewis Carroll defined as a portmanteau word; it is derived from the two words *purum uricum*.

[1] Horbaczewski, *Monatsh.*, 1882, **3**, 796; 1885, **6**, 356; 1887, **8**, 201, 584; Behrend and Roosen, *Ber.*, 1888, **21**, 999; *Annalen*, 1889, **251**, 235; Traube, *Ber.*, 1900, **33**, 1371, 3035; Fischer and Ach, *Ber.*, 1895, **28**, 2473; Fischer, *Ber.*, 1897, **30**, 559.

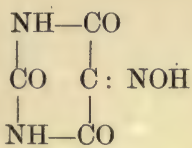


Barbituric acid.

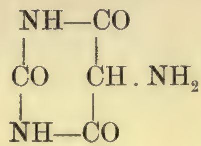
If we treat barbituric acid with nitrous acid, the methylene group is replaced by the isonitroso-radicle in the usual way, giving us oximido-malonyl-urea, which is also called violuric acid; and on reduction of this substance the oximido group is converted into an amido-radicle, producing amido-malonyl-urea, or uramil—



Barbituric acid.

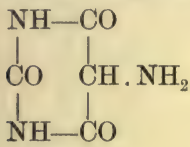


Violuric acid.

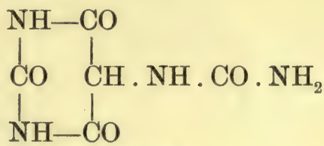


Uramil.

On treatment with potassium cyanate, uramil takes up cyanic acid and is changed into pseudo-uric acid—

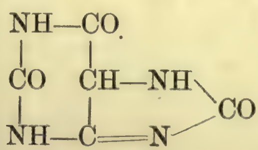


Uramil.

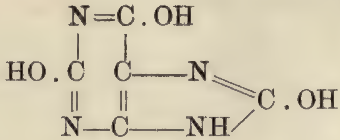


Pseudo-uric acid.

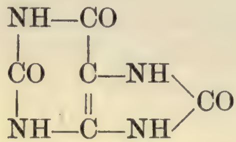
It is very hard to extract water from pseudo-uric acid, but this can be done by heating it with molten oxalic acid or by boiling it with hydrochloric acid. Under these circumstances one molecule of water is lost and uric acid is formed. Uric acid should therefore have the following constitution:—



Its property of forming salts could be ascribed to the existence of an enolic form, such as—

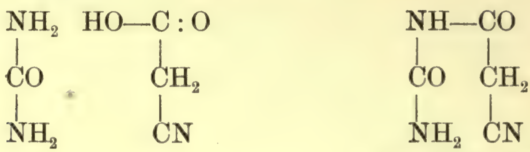


It is more usual, however, to consider uric acid to exist in the isomeric form—



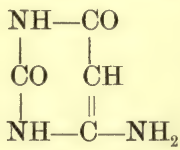
Uric acid.

The second synthesis takes as its starting-point the condensation of urea with cyanacetic acid, which takes place under the influence of phosphorus oxychloride—



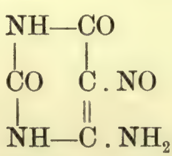
Cyanacetyl-urea.

Caustic soda causes cyanacetyl-urea to undergo an intramolecular change by which it is converted into amido-uracil—

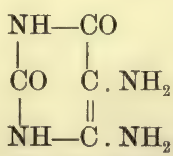


Amido-uracil.

When this is treated with nitrous acid it gives a nitroso compound which can be reduced with ammonium sulphide to diamido-uracil—

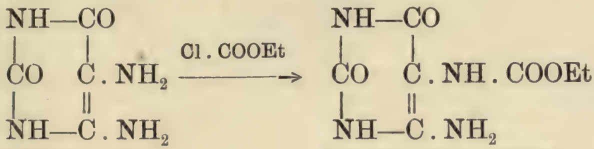


Nitroso compound.



Diamido-uracil.

The next step is to treat this diamido-derivative with caustic potash and chloroformic ester, by which means a urethane is formed—



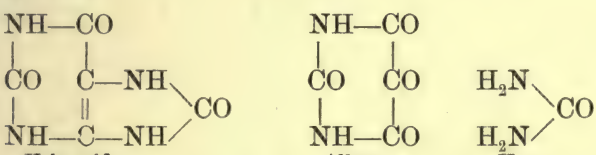
Diamido-uracil. Diamido-uracil urethane.

By heating the sodium salt of this substance to 180°-190° C. we obtain the sodium salt of uric acid.

By adapting this last synthesis we can obtain many uric acid derivatives; for we may use substituted ureas instead of the parent substance, or we may replace the urea by guanidine, or, lastly, we may discard the chloroformic ester in favour of formic ester.

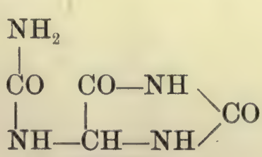
Before leaving the question of uric acid we must glance for a moment at the behaviour of that substance when treated with various oxidizing agents.

When the oxidation is carried out by means of cold nitric acid, the six-membered ring of uric acid remains intact, while urea is split off. The oxidized ring which remains can be derived from mesoxalic acid and urea; it is termed alloxan, or mesoxalyl-urea—



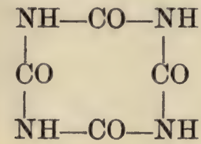
Uric acid. Alloxan. Urea.

If, on the other hand, we use alkaline potassium permanganate solution as our oxidizing agent, the five-membered ring remains unbroken, while the six-membered one is destroyed. The first products in this case are two substances, uroxanic acid, $C_5H_8N_4O_6$, and oxonic acid, $C_4H_5N_3O_4$, which are further oxidized to allantoin—



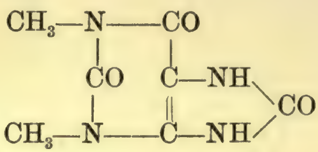
Allantoin.

With hydrogen peroxide the sodium salt of uric acid yields a substance of the formula $C_4H_4N_4O_4$, tetracarbonimide, which acts as a weak tetra-basic acid; on this account the following formula has been tentatively ascribed to it:—

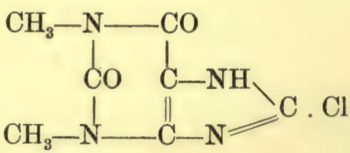


2. *The Synthesis of Theophylline.*

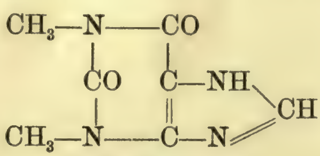
If in the uric acid syntheses we substitute symmetrical dimethyl-urea for the parent substance, we obtain in the end dimethyl-uric acid—



When this is treated with trichloride and oxychloride of phosphorus at 150° C. it is converted into a substance chlorotheophyllin, one atom of chlorine replacing a hydroxyl group. Chlorotheophylline must, therefore, have the following constitution:—



By reducing with hydriodic acid, theophylline[1] is formed—

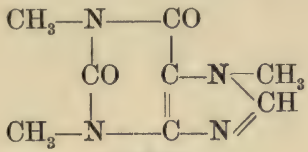


Theophylline.

[1] Fischer and Ach, *Ber.*, 1895, **28**, 3135.

3. *The Synthesis of Caffeine.*

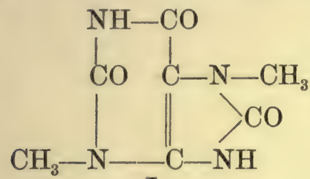
Caffeine[1] is obtained by the action of methyl iodide upon theophylline. Its constitution is therefore expressed by—



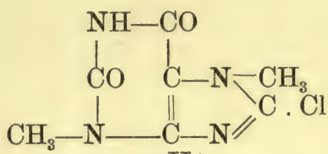
Caffeine.

4. *The Synthesis of Theobromine.*

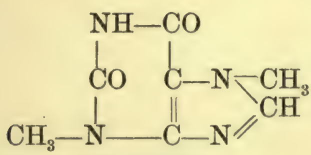
If we take as a starting-point the dimethyl-uric acid which has the constitution (I.) shown below, and treat it with phosphorus oxychloride, we shall find that it gives chlorotheobromine (II.), which, on reduction with hydriodic acid, yields theobromine (III.).[2] The reactions are parallel to those which lead from the isomeric dimethyl-uric acid to theophylline—



(I.)



(II.)



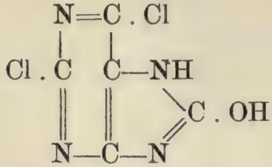
Theobromine.

(III.)

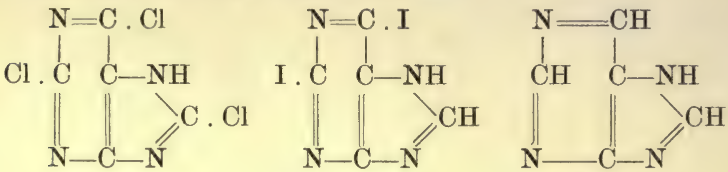
5. *The Synthesis of Purine.*

When the sodium salt of uric acid is treated with oxychloride of phosphorus it yields a hydroxy-dichloro-purine of the following formula :—

[1] Fischer and Ach, *Ber.*, 1895, **28**, 3135.
[2] Fischer, *Ber.*, 1897, **30**, 1839.

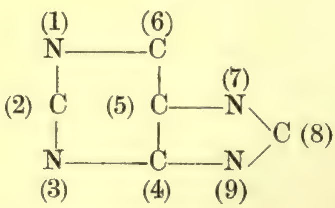


This, by means of trichloride of phosphorus, can be changed into a trichloro derivative, the third hydroxyl group being replaced by a chlorine atom. The substance thus formed, trichloropurine, is then treated with hydriodic acid at 0° C. whereby di-iodopurine is produced. This, by reduction with water and zinc dust, gives purine itself—



Trichloropurine. Di-iodopurine. Purine.

Purine is the substance to which all the substances of the purine group are usually referred; the derivatives being distinguished by means of the system of numbering shown in the following scheme:—



According to this, the substance xanthine is 2, 6-dihydroxy-purine; theophylline would be 1, 3-dimethyl-xanthine; caffeine would be 1, 3, 7-trimethyl-xanthine; theobromine would be 3, 7-dimethyl-xanthine; and uric acid 8-hydroxy-xanthine.

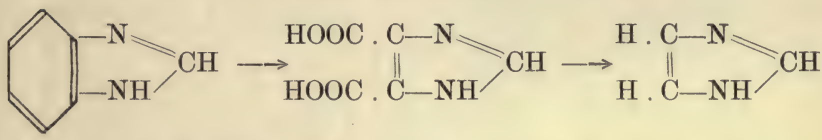
H.—The Glyoxaline Group.

In recent years a fresh nucleus, glyoxaline, has been detected among the basal substances of some of the alkaloids. Glyoxaline itself is metameric with pyrazole; and it may be

regarded as a pyrrol nucleus wherein one of the methine radicles is replaced by a nitrogen atom.

The parent substance of the glyoxaline group may be obtained by condensing together glyoxal, ammonia, and formaldehyde:—

It may also be produced by oxidizing benzimidazole with permanganate and then heating the dicarboxylic acid so formed—



An examination of the purine structure will show that it may be regarded as containing a glyoxaline ring condensed with a pyrimidine nucleus; so that the purine derivatives may be considered as partly derived from glyoxaline: but it is not necessary to lay too much stress upon this relationship since the uric acid group is sufficiently distinct to permit of its being regarded as a class by itself.

1. *The Constitution of Pilocarpine.*

Pilocarpine occurs in jaborandi leaves in conjunction with several related alkaloids: pilocarpidine,[1] isopilocarpine,[2] pilosine,[3] ψ-pilocarpine,[4] and ψ-jaborine.* The general structure of pilocarpine has been established in the following manner:—

The composition of pilocarpine is $C_{11}H_{16}N_2O_2$. Although it contains two nitrogen atoms it does not yield an amide with acetyl chloride; so it is clear that both nitrogen atoms must be tertiary ones. Oxidation[5] with permanganate produces

[1] Harnack, *Annalen*, 1887, **238**, 230.

[2] Petit and Polonowsky, *J. Pharm. Chim.*, (vi.), 1897, **5**, 370, 430; **6**, 8.

[3] Pyman, *Proc.*, 1912, **28**, 267.

[4] Petit and Polonowsky, *Chem. Zentr.*, 1897, (i.), 1126.

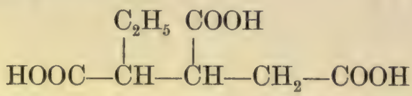
[5] Jowett, *Trans.*, 1900, **77**, 474, 851; 1901, **79**, 581, 1331; compare Pinner, *Ber.*, 1900, **33**, 1424, 2537; 1901, **34**, 727; 1902, **35**, 204, 2443; 1905, **48**, 1510.

* The supposed alkaloid jaborine appears to be a mixture (Jowett, *Trans.*, 1900, **77**, 474, 851; 1901, **79**, 581, 1331).

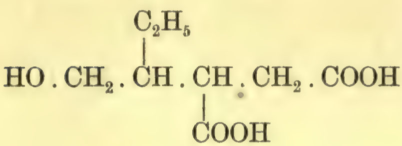
from pilocarpine a mixture of methyl-urea, homopilopic acid, and pilopic acid. As pilopic acid is derived from homopilopic acid by further oxidation, it will be best to examine first the constitution of homopilopic acid.

Homopilopic acid is a lactonic acid, containing one lactone ring and one free carboxyl radicle. From the stability of the lactonic structure, the substance is evidently a γ-lactone. Its composition is $C_8H_{12}O_4$.

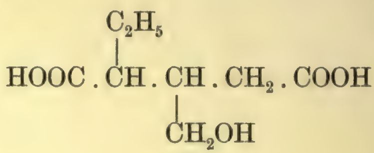
When fused with caustic potash, homopilopic acid gives α-ethyltricarballylic acid:—



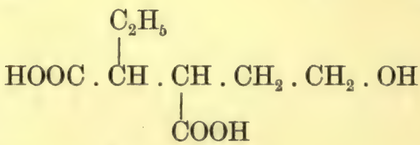
This substance must arise from a hydroxy-acid by the action of the potash; and for this hydroxy-acid three formulæ are possible, from which we must select the correct one:—



(I.)

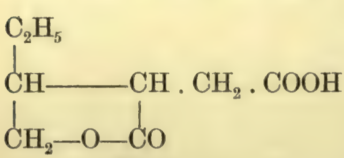


(II.)

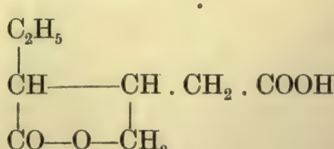


(III.)

Now pilopic acid appears to be derived from homopilopic acid by loss of carbon dioxide and oxidation of the carbon atom which carried the destroyed carboxyl radicle. Of all the possible γ-lactonic formulæ derived from the three acids shown above, only two can fulfil this condition—

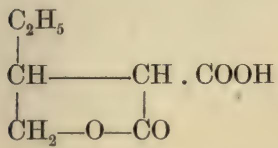


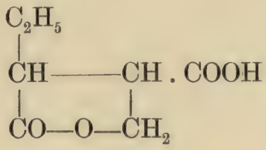
(A.)



(B.)

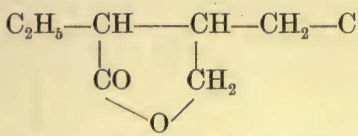
The corresponding formulæ for pilopic acid would therefore be—


(a.)


(b.)

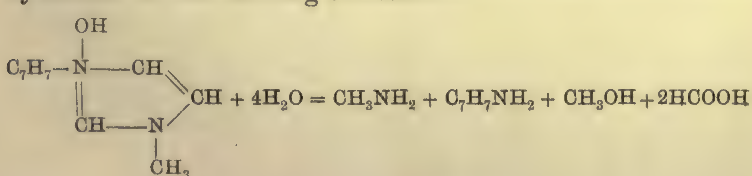
Now, owing to the fact that in (a) there are two carboxyl radicles (one in lactone form) attached to the same carbon atom, we should expect such a compound to lose carbon dioxide easily on heating as malonic acid does. Pilopic acid, however, is stable even at 200° C. It seems most probable, therefore, that pilopic acid has the formula (b); which leads us to the formula (B) for homopilopic acid.

By this reasoning, pilocarpine itself must contain the skeleton

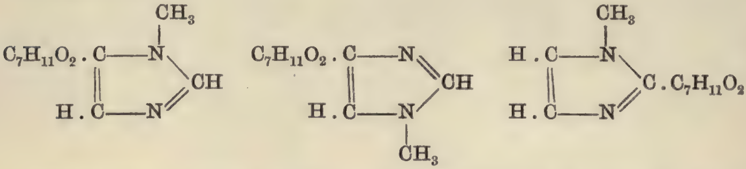


in addition to a group $C_3H_5N_2$, which disappears completely on oxidation. With regard to the structure of this last complex we must look for further evidence.

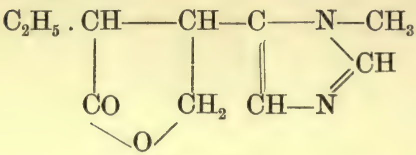
When derivatives of glyoxaline are allowed to interact with alkyl halides, ammonium compounds are formed which break down under the action of caustic potash, yielding primary amines. Now when pilocarpine is submitted to this series of reactions, it gives rise to equimolecular quantities of methylamine, methyl alcohol, and $C_7H_7 . NH_2$, plus two molecular proportions of formic acid. This decomposition can be accounted for by assuming that its methyl iodide addition product is transformed by caustic potash into an ammonium hydroxide of the following structure:—



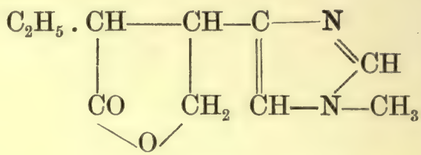
Thus pilocarpine itself may have one of the following structures :—*



The exact constitution of pilocarpine is not yet defined; but as far as the evidence at our disposal is concerned either the formula proposed by Pinner and Schwarz[1] or that suggested by Jowett[2] suffices to account for the reactions of the compound—



Pinner's formula.



Jowett's formula.

2. *Isopilocarpine and Pilosine.*

The oxidation of pilocarpine and isopilocarpine gives rise to the same products; which shows that the two substances are closely allied in structure. Their chemical properties are also very similar; and the absorption spectra of their nitrates are identical.[3] Further, pilocarpine and isopilocarpine, when treated with alcoholic potash, are both converted into an equilibrium mixture containing chiefly isopilocarpine. From evidence of this kind, Jowett[4] regards isopilocarpine as a stereo-

* It is assumed that the union between the glyoxaline group and the rest of the molecule is originally through carbon, a wandering of the homopilopic group taking place to the nitrogen during the decomposition.

[1] Pinner and Schwarz, *Ber.*, 1902, **35**, 2441; Pinner, *ibid.*, 1905, **48**, 1510.

[2] Jowett, *Trans.*, 1903, **83**, 442; 1905, **87**, 794; Pyman, *Trans.*, 1910, **97**, 1814.

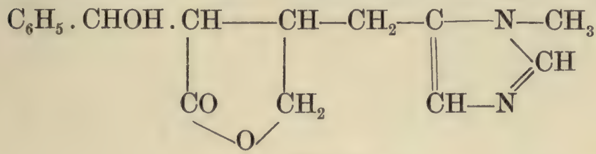
[3] Dobbie, *cf.* Hartley, *Proc. Chem. Soc.*, 1903, **19**, 122.

[4] Jowett, *Trans.*, 1903, **83**, 438; 1905, **87**, 794.

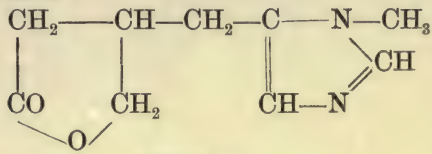
[5] *Ibid.*

isomer of pilocarpine; and this view appears to cover all the more important reactions of the alkaloids.

The constitution of pilosine has been investigated by Pyman.[1] He finds that on distillation with potash solution it yields benzaldehyde and a substance called pilosinine, which closely resembles pilocarpine in physiological action. He ascribes to the two substances the following structures:—



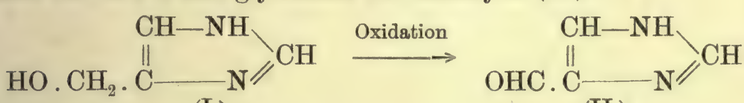
Pilosine.



Pilosinine.

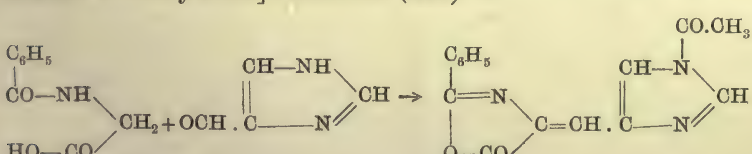
3. *The Synthesis of Histidine.*

By heating together potassium thiocyanate and the hydrochloride of diamido-acetone, amido-methyl-glyoxaline mercaptan is produced; and when this is added to dilute nitric acid, it yields 4-hydroxymethyl-glyoxaline (I.) which forms the raw material of the histidine synthesis.[2] Oxidation with chromic acid converts it into glyoxaline formaldehyde (II.)—



(I.) (II.)

By means of acetic anhydride, the formaldehyde derivative is condensed with hippuric acid to form 2-phenyl-4-[1-acetyl-glyoxaline-4-methylidine]-oxazolone (III.):—



Hippuric acid. (II.) (III.)

[1] Pyman, *Proc.*, 1912, **28**, 267.

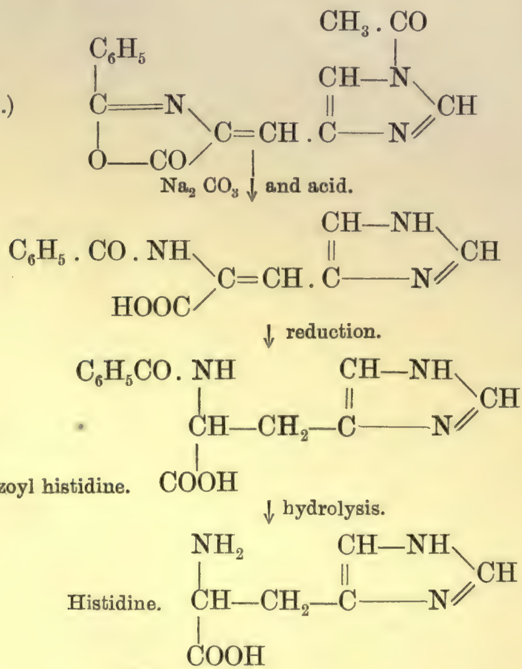
[2] *Ibid.*, *Trans.*, 1916, **109**, 186.

When this oxazolone derivative is boiled with very dilute sodium carbonate solution, the acetyl group is split off and the oxazolone ring opens. If, now, the calculated quantity of an acid be added, the compound (IV.) results. Reduction of this produces benzoyl-histidine (V.) from which histidine itself is obtained by hydrolysis—

(III.)

(IV.)

(V.)



Benzoyl histidine.

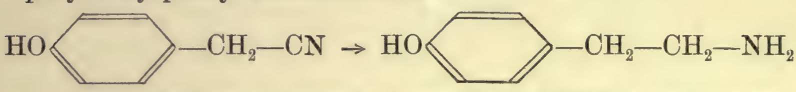
Histidine.

I.—Some Derivatives of Ergot and their Allies.

The examination of ergot has resulted in the discovery in it of numerous compounds of physiological interest, for several of its products have marked influence upon the blood pressor system and in other directions as well. Though all the substances with which we are about to deal are not strictly alkaloids within the definition which was given at the beginning of this chapter, it seems desirable to strain a point and include them in this survey rather than omit to mention them on grounds of mere punctiliousness.

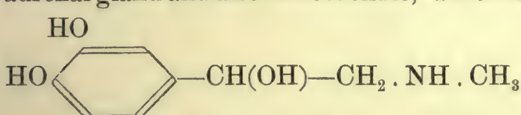
Tanret[1] discovered an active principle in ergot; but it was not until further work had been done by Barger and Carr[2] that the composition of the materials was made clear. The last two authors isolated two substances, ergotoxine, $C_{35}H_{41}O_6N_5$, and ergotinine, $C_{35}H_{39}O_5N_5$. It will be noticed that ergotoxine contains a molecule of water more than ergotinine; and subsequent investigation[3] proved that ergotinine is the lactone of ergotoxine, which is therefore a carboxylic acid. Both ergotoxine and ergotinine give on destructive distillation isobutyryl-formamide, $(CH_3)_2CH . CO . CO . NH_2$. Beyond this, nothing definite is known as to their constitution.

Further examination of ergot[4] brought to light another physiologically active substance, *p*-hydroxy-phenyl-ethylamine. This compound is also found in putrid meat.[5] It has been synthesized by the reduction, with sodium and alcohol, of *p*-hydroxy-phenyl-acetonitrile :—

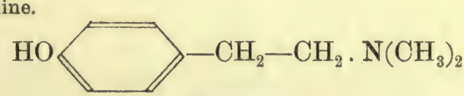


It has also been obtained in even better yield by acting on anisaldehyde, $CH_3O . C_6H_4 . CHO$, with nitromethane to form $CH_3O . C_6H_4 . CH : CH . NO_2$, which is then reduced to the amine. Demethylation of the methoxy-group completes the process.[6]

The structure of this substance is interesting, since its skeleton occurs in adrenaline,[7] the active principle of the adrenal gland and also in hordenine,[8] which is present in barley—



Adrenaline.



Hordenine.

[1] Tanret, *Compt. rend.*, 1875, **81**, 896; 1878, **86**, 888; *Ann. Chim. Phys.*, 1879, (v.), **17**, 493.

[2] Barger and Carr, *Trans.*, 1907, **91**, 336.

[3] Barger and Ewins, *Trans.*, 1910, **97**, 284.

[4] Barger, *Trans.*, 1909, **95**, 1123.

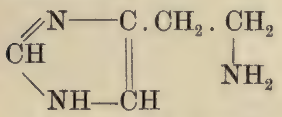
[5] Barger and Walpole, *J. Physiol.*, 1909, **38**, 343.

[6] Rosenmund, *Ber.*, 1909, **42**, 4778.

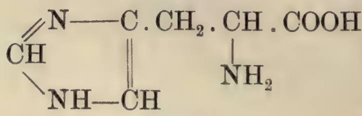
[7] Jowett, *Trans.*, 1904, **85**, 192.

[8] Léger, *Compt. rend.*, 1906, **142**, 108; **143**, 234, 916.

Yet another active substance[1] was found in ergot: 4-β-amino-ethyl-glyoxaline, which is obviously closely related to histidine—



4-β-amino-ethyl-glyoxaline.



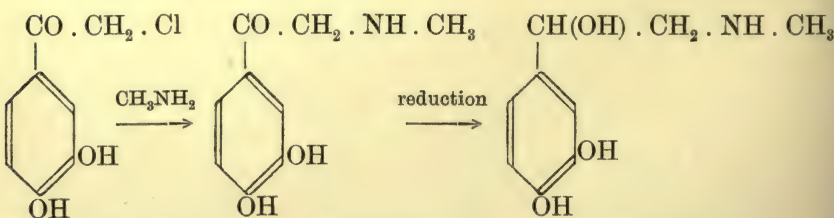
Histidine.

Finally, a substance agmaline[2] has been extracted from ergot; and it is found that it is related to the naturally occurring amino-acid arginine in exactly the same way as the glyoxaline derivative mentioned above is related to histidine—

Agmaline $NH:C(NH_2).NH.(CH_2)_3.CH_2.NH_2$
Arginine $NH:C(NH_2).NH.(CH_2)_3.CH(NH_2).COOH$

It may be well to give the syntheses of adrenaline and hordenine; since both these substances are of interest not only on account of their physiological properties but also owing to their structural relationship to the ergot derivatives.

Adrenaline has been synthesized in the following way.[3] Catechol is treated with chloracetyl chloride to produce chloracetyl catechol (I.). The action of methylamine converts this into the ketone adrenalone (II.), which can be reduced electrolytically, or by the use of aluminium amalgam, to adrenaline (III.)—



Chloracetyl catechol. (I.) Adrenalone. (II.) Adrenaline. (III.)

[1] Barger and Dale, *Trans.*, 1910, **97**, 2592.
[2] Engeland and Kutscher, *Zentr. Physiol.*, 1910, **24**, 479.
[3] Stolz, *Ber.*, 1904, **37**, 4149; Dakin, *Proc. Roy. Soc.*, 1905, **76**, (B), 491.

Another method takes as its starting-point protocatechuic aldehyde. This is subjected to the cyanhydrin reaction and the cyanhydrin so formed is reduced to an amine. Methylation of the amino-group yields adrenaline. The compound formed in each case is the racemic base, from which the antipodes can be obtained by resolution of the tartrates.

Since hordenine is the dimethyl derivative of *p*-hydroxy-phenyl-ethylamine, it might be supposed that the latter would be used as a starting-point in the hordenine synthesis. Owing, however, to the readiness with which hordenine, when formed, passes into the tetra-alkyl ammonium salt form, it is found better to set out from phenyl-ethyl alcohol. This substance is converted into the corresponding chloride which, when treated with dimethyl-aniline, yields the base $C_6H_5 . CH_2 . CH_2 . N(CH_3)_2$. The missing hydroxyl radicle in the para-position is introduced by nitration, reduction, and diazotization in the usual manner. Another method consists in the methylation of *p*-methoxy-phenyl-ethylamine followed by the action of hydriodic acid, which splits off the methyl radicle of the methoxy-group.

With regard to the effect of structure upon physiological properties, it is interesting to note that the conversion of the alcohol adrenaline into the ketone adrenalone does not destroy the physiological activity; nor is the presence of the methyl radicle attached to the nitrogen atom essential. One hydroxyl radicle in the benzene nucleus appears to be sufficient. A marked influence is exerted by the introduction of a methyl radicle in the α- or β-position; for compounds containing this grouping are much less active than the parent compounds.

CHAPTER VII.

THE POLYPEPTIDES.[1]

1. *The Albumins and their Decomposition Products.*

WHEN we examine the contents of the cells from which living tissues are built up, we find that they are for the most part composed of albuminous bodies of extremely complicated chemical character. These albumins are distinguished from all the other naturally occurring substances by the fact that animal life may be supported upon them alone in conjunction with water and salt; whereas fats and carbohydrates do not in themselves furnish nourishment sufficient for the support of animal functions for an indefinite period. The importance of the albumins from the physiological point of view, therefore, can hardly be over-estimated; while from the chemical side they furnish one of the most difficult and complicated problems which the organic chemist has yet attacked.

The difficulties of the researches which have been carried out in this branch of organic chemistry can hardly be over-estimated. In the first place, many albumins are non-crystalline substances which require special treatment before they can be obtained in crystalline form; this, of course, makes it very difficult to determine the state of purity of any specimen under consideration. Secondly, the extreme sensitiveness of albumins to heat, acids, or alcohol renders them very liable to be altered during the progress of the ordinary chemical reactions. Again, the molecular complication of these substances must be tremendous, if we are to judge from molecular weight

[1] A complete set of references up to 1906 will be found in a lecture by Fischer (*Ber.*, 1906, **39**, 530). See also Fischer, *Ber.*, 1906, **39**, 2893; 1907, **40**, 1754, 3704; 1908, **41**, 850, 2860; Fischer and Königs, *Ber.*, 1907, **40**, 2048; Fischer and Schulze, *ibid.*, 943; Fischer and Gerngross, *Ber.*, 1909, **42**, 1485; Fischer and Luniak, *ibid.*, 4752. Fischer's papers have been reprinted in his book *Die Aminosäuren, Polypeptide und Proteine* (1906).

determinations: egg albumin has been estimated to have a molecular weight of at least 15,000, according to the results of the freezing-point method.*

In the foregoing chapters we have dealt at some length with the constitutions of various compounds, and it will be remembered that there are two general methods of investigating the constitution of any given substance. We may attack the question from the synthetical side or from the analytical point of view: in the first case we study the general properties of the substance, then ask ourselves in what way we can build up a molecule whose reactions will resemble those of the one we are studying, and having synthesized this body we compare its reactions with those of the original; in the analytical method, we take the molecule to pieces in various ways, and isolate a series of decomposition products, from which we endeavour to guess the manner in which they were arranged in the original molecule. Now, in the case of the albumins, the first line of research turned upon the analytical results. This was to be foreseen, for it seemed almost impossible to build up molecules of such extreme complexity. The analytical method, however, has not carried us very far; and the most important researches on the question have been carried out from the synthetical side since Fischer attacked the problem. Before dealing with his work, however, we must cast a glance at the decomposition products which have been obtained from the albumin group.

The oxidation of the albumins cannot be said to have yielded results of any great interest; the major part of our knowledge of these bodies has been obtained by means of hydrolysis reactions. When ferments are allowed to act upon protein derivatives, the bodies first formed are albumoses and peptones. These intermediate compounds can be further broken down into amino-acids. Hydrolysis by means of alkali takes place more rapidly, while acids decompose the albumins most easily. It is thus made clear that the substances lying at the base of the albumins belong to the class of amino-acids; and, further, that these acid nuclei are linked together in some way which allows them to be separated one from another by means

* Owing to the colloidal nature of the albumins, it is unsafe to place too much reliance on the exactitude of these results.

of hydrolysis. It is evident that amide-formation is the most probable method of uniting the nuclei; and from this point of view Fischer took up the work of synthesizing some compounds which, while not themselves of the protein class, would show sufficient resemblance to the naturally occurring substances to allow us to deduce the probable constitution of at least part of the albumin molecule.

To describe these synthetic substances, Fischer proposed the name "*Polypeptides*," by which he intends to denote those compounds which are derived from two amino-acid molecules by the elimination of water. A few polypeptides have been obtained by the hydrolysis of proteins, but by far the greater number are synthetic. We may now give the outlines of the methods employed by Fischer in his researches.

2. *Methods of Synthesizing Polypeptides.*

As a first step in polypeptide syntheses, it was necessary to obtain mono-amino-acids. This Fischer did by means of the ordinary methods—action of ammonia on the esters of bromo-fatty acids or by Strecker's cyanhydrin method (addition of hydrocyanic acid and ammonia to an aldehyde and hydrolysis of the cyanhydrin thus formed). Now, having obtained these acids, another problem presents itself. If we combine together two racemic acids we shall have not a single reaction product, but a mixture of two new racemic substances. For instance, if we start with racemic alanine and racemic leucine, we should produce a mixture of the four isomers—

d-Alanine-*d*-leucine.	*d*-Alanine-*l*-leucine.
l-Alanine-*l*-leucine.	*l*-Alanine-*d*-leucine.

The two substances in the left-hand column then combine to form a racemic substance, and the two in the right-hand column to form *another* racemic compound, so that we should have two new bodies instead of a pure compound. And, of course, if we coupled together more than two racemic acids we should find the number of stereo-isomers in the product increased in like manner. This evidently threw considerable difficulty in the way, and to avoid it Fischer resolved to use in his condensations optically active acids only. By this means he excluded the possibility of racemic compounds being formed, so that from one pair of amino-acids he obtained only a single reaction product.

This did not clear the experimental difficulties away, however; it only carried them one step further back. For, owing to the very weak acidity of the amino-acids, resolution of these substances into their optically active antipodes by salt-formation with active bases was by no means an easy task. Fischer evaded this difficulty in turn by one of his usual simple artifices. He benzoylated the amino-group of the acid, and thus reduced its basic properties to a minimum; thereafter, resolution into the optical antipodes presented no difficulty, and after this had been accomplished, the benzoyl radicle was split off and the optically active amino-acid remained.

I. The first method employed by Fischer in the actual synthesis of polypeptides depends upon the elimination of a molecule of alcohol from two molecules of amino-ester—

$$\begin{aligned}&NH_2 . CH_2 . COOEt + NH_2 . CH_2 . COOEt\\&\qquad = NH_2 . CH_2 . CO . NH . CH_2 . COOEt + EtOH\end{aligned}$$

Now, it will be seen at once that if we applied this method as given above to a mixture of two different amino-acids, it would be sheer chance that would govern the production of the end-product. For example, if we were to combine together the two esters (A) and (B) we should get a mixture of (C) and (D) in the reaction product—

$$\begin{array}{ll}
\text{(A)} & NH_2 . CH_2 . COOEt \\
\text{(B)} & NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt \\
\text{(C)} & NH_2 . CH_2 . CO . NH . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt \\
\text{(D)} & NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CO . NH . CH_2 . COOEt
\end{array}$$

This difficulty in its turn was overcome by Fischer in a very simple manner. Before condensing the two substances together he allowed one of them to react with ethyl chlorocarbonate, which acted upon the amino-group and protected it from further attack—

$$\begin{aligned}&Cl . COOEt + NH_2 . CH_2 . COOEt\\&\qquad = EtOOC . NH . CH_2 . COOEt + HCl\end{aligned}$$

When a compound such as this is heated for thirty-six hours with the ester of an amino-acid, alcohol is eliminated between the $—NH_2$ group of the amino-acid and the $—CH_2 . COOEt$ group of the above substance, whose amino-group cannot react in this way. Thus we know at once the constitution of the resulting compound. An example will serve to make the matter clear. If we start with the substance glycyl-glycine,* and treat it with chloro-carbonic ester, we shall obtain the substance shown below, glycyl-glycine carboxylic acid ester—

$$EtOOC . Cl + NH_2 . CH_2 . CO . NH . CH_2 . COOEt$$
$$= EtOOC . NH . CH_2 . CO . NH . CH_2 . COOEt + HCl$$

When this substance is heated for thirty-six hours with leucine ester, ethyl alcohol is eliminated in the following way:—

$$EtOOC.NH.CH_2.CO.NH.CH_2.COOEt + NH_2.CH.(C_4H_9).COOEt$$
$$= EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH(C_4H_9).COOEt$$

This substance is the carboxylic ester of glycyl-glycine-leucine; as can be seen from the formulæ, it can have no other constitution than that shown. This carbethoxy-glycylglycyl-leucine ester contains three amino-acid nuclei, and is therefore called a tri-peptide derivative.

II. The yields of end-product from the foregoing method of synthesis were poor, and Fischer therefore turned to another way of attaining his objective. When the ester of the chloro-carbonic derivative of an amino-acid is treated with thionyl chloride, an acid chloride is formed; and this readily condenses with amino-esters, forming polypeptide derivatives. For instance, if we start again with the derivative obtained by the action of chlorocarbonic ester upon glycylglycine, and treat it with thionyl chloride, we shall produce the chloride whose constitution is shown below—

$$EtOOC . NH . CH_2 . CO . NH . CH_2 . CO . Cl$$

When this chloride is condensed with glycylglycine ester—

$$NH_2 . CH_2 . CO . NH . CH_2 . COOEt$$

it yields the tetra-peptide derivative, glycylglycylglycylglycine-carbethoxy-ester—

$$EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.COOEt$$

* Fischer terms "glycyl" the radicle $NH_2 . CH_2 . CO—$ which is derived from glycine (glycocoll) $NH_2 . CH_2 . COOH$.

III. The drawback of the two foregoing methods lies in the fact that, so far, no method has been discovered by means of which we can eliminate the group —COOEt, which is attached to one end of the polypeptide chain; so that neither method can be employed to build up a true polypeptide. Fischer therefore devised another method by means of which the polypeptides themselves can be produced. Starting from the ester of a substance like glycine (I.) or glycylglycine, he treated this with chloracetyl chloride (II.) or some similar compound. Hydrochloric acid is eliminated, and the two molecules combine together to form a compound with chlorine at one end of the chain (III.). The ester group at the other end of the chain is then hydrolyzed very carefully, and a chloro-acid produced (IV.), which, on treatment with ammonia, yields a true polypeptide (V.)—

$$\begin{array}{rl} \text{(I.)} & NH_2 . CH_2 . COOEt \\ \text{(II.)} & Cl . CH_2 . CO . Cl \\ \text{(III.)} & Cl . CH_2 . CO . NH . CH_2 . COOEt \\ \text{(IV.)} & Cl . CH_2 . CO . NH . CH_2 . COOH \\ \text{(V.)} & NH_2 . CH_2 . CO . NH . CH_2 . COOH \end{array}$$

The reason for hydrolyzing the ester (III.) to the acid (IV.) lies in the fact that if this were not done an amide would be formed on treatment with ammonia, and the amido-group would be most difficult to get rid of later.

IV. A variation of the previous method may also be used. If we take the substance—

$$Cl . CH_2 . CO . NH . CH_2 . COOH$$

which was formed in the course of the last synthesis we described, and treat it with pentachloride of phosphorus, we convert the acid into the chloride *—

$$Cl . CH_2 . CO . NH . CH_2 . CO . Cl$$

which can then be made to interact with glycine ester, yielding the more complicated substance—

$$Cl . CH_2 . CO . NH . CH_2 . CO . NH . CH_2 . COOEt$$

* Thionyl chloride is a better reagent than phosphorus pentachloride for producing acid chlorides. The reaction takes place according to the equation—

$$R . COOH + SOCl_2 = R . CO . Cl + SO_2 + HCl$$

from which it will be clear that the acid chloride can be obtained pure simply by boiling off the sulphur dioxide and hydrochloric acid.

The remaining chlorine atom may then be replaced by the amino group by means of ammonia; and after hydrolysis of the ester group the tri-peptide glycylglycylglycine is formed—

$$NH_2 . CH_2 . CO . NH . CH_2 . CO . NH . CH_2 . COOH$$

V. This modification has been further extended. When amino acids are treated with a mixture of acetyl chloride and phosphorus pentachloride, the corresponding acid chlorides are formed. These can be combined with other amino-acids, and in this way we can obtain polypeptides. For instance, if we take glycine and treat it as described we should expect to produce glycyl chloride—

$$NH_2 . CH_2 . COOH \rightarrow NH_2 . CH_2 . CO . Cl$$

This can be condensed with another molecule of glycine, forming glycylglycine—

$$\begin{aligned} &NH_2 . CH_2 . CO . Cl + NH_2 . CH_2 . COOH \\ &\qquad = NH_2 . CH_2 . CO . NH . CH_2 . COOH \end{aligned}$$

VI. If we abstract two molecules of alcohol from two molecules of an α-amino-ester, a cyclic substance is produced, which is a derivative of $\alpha\gamma$-diketo-piperazine—

$$\begin{array}{l} CH_2—NH_2 \\ | \\ CO—OEt \end{array} + \begin{array}{r} EtO—CO \\ | \\ H_2N—CH_2 \end{array} = \begin{array}{lr} CH_2—NH—CO & \\ | & | \\ CO—NH—CH_2 & \end{array} + 2EtOH$$

This cyclic compound, when carefully treated with hydrochloric acid, can be opened out into an open-chain body, glycylglycine—

$$\begin{array}{lr} CH_2—NH—CO & \\ | & | \\ CO—NH—CH_2 & \end{array} + H_2O = \begin{array}{lr} CH_2—NH_2 & COOH \\ | & | \\ CO—NH—CH_2 & \end{array}$$

By choosing the appropriate amino-ester from which to start, a given polypeptide may be obtained in this manner.

We cannot go into details with regard to the various substances which have been synthesized by means of the foregoing methods, but there is one substance which is worthy of mention. Fischer has recently synthesized an octadeca-peptide in the following manner. Starting from dextro-α-bromo-isocapronyl-diglycylglycine—

$$\begin{array}{l} Br . \underset{\displaystyle C_4H_9}{\underset{|}{CH}} . CO . (NH . CH_2 . CO)_2 . NH . CH_2 . COOH \end{array}$$

he treated this according to the fourth method, combining it with penta-glycylglycine, and, finally, exchanging the bromine atom for an amino-group, he obtained lævo-leucyl-octaglycyl-glycine—

$$\underset{\displaystyle C_4H_9}{\underset{|}{NH_2 . CH}} . CO . (NH . CH_2 . CO)_8 . NH . CH_2 . COOH$$

This polypeptide was then coupled with dextro-bromo-isocaproyl-diglycylglycine, and again treated with ammonia, whereby the tetradecapeptide shown below was formed—

$$\underset{\displaystyle C_4H_9}{\underset{|}{NH_2CH}}.CO.(NH.CH_2 . CO)_3 . NH . \underset{\displaystyle C_4H_9}{\underset{|}{CH}} . CO . (NH . CH_2 . CO)_8.NH.CH_2 . COOH$$

Lævo-leucyl-triglycyl lævo-leucyl-octaglycyl-glycine.

By a repetition of this series of reactions the octadecapeptide was formed, which has the constitution shown below—

$$\begin{array}{l} NH_2.CH(C_4H_9).CO.(NH.CH_2.CO)_3.NH.CH(C_4H_9).CO.(NH.CH_2.CO)_3.NH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | \\ \qquad\qquad\qquad\qquad\qquad HOOC.CH_2.NH.(CO.CH_2.NH)_8.CO.CH.C_4H_9 \end{array}$$

l-Leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine.

This extraordinary substance is apparently one of the most complicated systems of known constitution which has hitherto been synthesized. Its molecular weight is 1213, while that of the fairly complicated natural body, tri-stearin, is only 891.

3. *The Polypeptides and the Proteins.*

We must now briefly summarize the main characteristics of the polypeptide class, and it may be of interest to compare them with those of the naturally occurring proteins. The polypeptides are solids, which usually melt at about 200° C., with some decomposition. They are easily soluble in water, but insoluble in alcohol, like some of the albumins; and instead of having the usual insipid or sweet taste of the ordinary amino-acid, they are bitter, like the protein derivatives. In dilute sulphuric acid solution they are precipitated by phosphotungstic acid, in which behaviour they resemble the albumins. Both the natural and artificial classes give the biuret reaction. The action of ferments, or of acids or alkalis, is the same in both classes; and similar products are obtained when animals are fed with polypeptides and albumins. In the case of ferment action it is found that much depends upon the groups which

have been used in building up the polypeptide structure, some polypeptides being much more easily fermented than others.

From these data it will be obvious that the researches of Fischer and Curtius have carried us into a series of substances which, in many respects, resemble the natural bodies of the protein class; how far the parallel holds good, and how high in the scale we can carry our syntheses remains for the future to make clear.

CHAPTER VIII.

THE CHLOROPHYLL PROBLEM.

1. *Introductory.*

THE chemical constitution of the green colouring matter of plants offers a problem which has taxed the ingenuity of many investigators. Even so recently as five years ago our knowledge of the chlorophyll structure was so fragmentary and disconnected that the very name of the substance was omitted from standard textbooks. But since then the compound has been submitted to rigorous scrutiny, its reactions have been classified, its decomposition products brought into relation to each other; and although our views on the exact nature of its structure are still fluid, the information at our disposal is sufficient to render a coherent account of it possible.[1]

In the present chapter an attempt will be made to link together the scattered data of the subject in a more or less connected scheme;* and to present to the reader a summary of the important information which has been acquired. In this branch of chemistry, theory has in many cases far outrun practice; and constitutional formulæ have been proposed for some substances the true structures of which are possibly different from those assumed for them. Under these circumstances an endeavour will be made here to indicate as clearly as possible the points at which established facts end and pure hypotheses begin; for it seems desirable to draw the line of demarcation as sharply as can be done. Some of the formulæ ascribed to certain compounds may be accurate, though yet unproved; but it would be doing the reader a poor service to

[1] For a general account of recent researches by Willstätter, see *Ber.*, 1914, **47**, 2831.

* The reader is advised to make use of the table at the end of this volume in any difficulty which may arise as to the relations between certain chlorophyll derivatives.

leave him in doubt as to their actual present value, or to try to persuade him into an acceptance of constitutions which later work may prove to be erroneous.

A study of the literature on chlorophyll is beset with difficulties. In the first place, the nomenclature of the subject is to a large extent new and different from that with which the organic chemist is familiar; for instead of referring to acids in the usual terms, the investigators have christened them with a brand-new set of names; and as these titles have established themselves in the literature, it is hopeless to expect that they will be altered now. Secondly, chlorophyll contains within its molecule a complex and sensitive grouping capable of undergoing various intramolecular changes under the action of reagents; and these rearrangements form one of the most puzzling factors in the problem.

The extraction of chlorophyll from plants is a simple operation. The leaves are removed from their stems, dried and powdered. Alcohol is then poured over the powder and the mixture kept constantly stirred. After a longer or shorter time the chlorophyll passes into the liquid, from which it can be extracted. By this process a "crystalline chlorophyll" is obtained; whereas when ether is substituted for alcohol, an "amorphous chlorophyll" is found in solution.[1]

The composition of "amorphous chlorophyll" may be regarded provisionally as corresponding to $C_{55}H_{72}N_4O_5Mg$; but even here a word of caution is desirable. The lowest possible molecular weight of a substance such as this would reach nearly 900; and reflection will show that the exact analysis of so complex a compound must be difficult in the extreme.

The complication of the formula makes it obvious that our chief knowledge of chlorophyll must be gained through an acquaintance with its degradation products. Three main types of reaction might be employed to break down the chlorophyll molecule: oxidation, reduction, and hydrolysis. In practice, it has been found that most information is gained from a study of the last class; for oxidation and reduction proved to be comparatively useless in so far as the production of immediate decomposition products is concerned.

[1] Willstätter and Benz, *Annalen*, 1908, **358**, 267; Willstätter and Oppé, *ibid.*, 1911, **378**, 1.

Along with chlorophyll, two other colouring matters are found in leaves. The one, carotin, is coppery in colour and is identical with the substance which gives their colour to carrots. It is a hydrocarbon of the composition $C_{40}H_{56}$. The other colouring material, xanthophyll, is dark brown-red in tint; has the composition $C_{40}H_{56}O_2$; and seems to be an oxidation product of carotin.[1] It is suggested that in summer the green of chlorophyll masks the tints of carotin and xanthophyll; but when in autumn the chlorophyll decays, the reddish pigments become visible and give the leaves their autumn colouring.

It is interesting to note that the chlorophyll of brown algæ is identical with that derived from land-plants,[2] a fact which appears most unexpected from the tints of the organisms.

2. *Amorphous Chlorophyll and so-called "Crystalline Chlorophyll".*

As has been pointed out already, the extraction of chlorophyll from plants by means of ether yields an amorphous substance. Specimens of this amorphous product were obtained, under carefully regulated conditions, from about two hundred different kinds of plants; and, on examination, it was found that all the samples yielded on decomposition approximately the same amount—about 30 per cent.—of an alcohol named phytol.[3] This at once suggests that amorphous chlorophyll may be the phytyl ester of some unknown acid.

Confirmation of this view was obtained by hydrolyzing amorphous chlorophyll with cold dilute potash. The products of the reaction are equimolecular quantities of methyl alcohol, phytyl alcohol, and the potassium salt of a tribasic acid, which is termed chlorophyllin.[4] It appears, then, that amorphous chlorophyll is a di-ester of this tribasic acid, chlorophyllin, in which one of the carboxyl groups is esterified with methyl alcohol, another with phytyl alcohol, whilst the third is occupied in some other manner.

[1] Willstätter and Mieg, *Annalen*, 1907, **355**, 1.

[2] Willstätter and Page, *Annalen*, 1914, **404**, 237.

[3] Willstätter, Hocheder, and Hug, *Annalen*, 1909, **371**, 1; Willstätter and Oppé, *ibid.*, 1911, **378**, 1.

[4] Willstätter and Stoll, *Annalen*, 1910, **378**, 18.

But three carboxyl radicles would imply the presence of six oxygen atoms in the chlorophyll molecule; whereas from the analytical results there appear to be only five. The possibility of internal anhydride formation is excluded by the fact that phytochlorin-*e* (a decomposition product of chlorophyll) contains the same grouping and does not form an amide with ammonia.[1] Since nitrogen atoms are found in the molecule, it might be assumed that the third acidic group is present as an amide; but in this case, ammonia would be found in the products of hydrolysis. The only feasible explanation is that the fifth oxygen atom of amorphous chlorophyll forms part of a lactam ring which is opened up on hydrolysis, setting free the third carboxyl group.[*]

Now since phytyl alcohol has the formula $C_{20}H_{39}OH$, it follows that on the above assumption we can express the hydrolysis reaction thus—

$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l} =N \\ \quad | \\ -CO \\ -COOCH_3 \\ -COOC_{20}H_{39} \end{array}\right. \xrightarrow{\text{Hydrolysis}} C_{31}H_{30}N_3Mg\left\{\begin{array}{l} =NH \quad + CH_3OH \\ -COOK \\ -COOK \\ -COOK + C_{20}H_{39}OH \end{array}\right.$$

Amorphous chlorophyll. Chlorophyllin salt. Phytol.

The case of "crystalline chlorophyll" must now be examined. It also is found to be a di-ester; but instead of the phytyl radicle it contains an ethyl group; the second carboxyl radicle is esterified with methyl alcohol; whilst the third carboxyl resembles the corresponding one of amorphous chlorophyll. Thus, during the extraction of chlorophyll with alcohol, it is clear that the phytyl group has been replaced by an ethyl radicle. This process is traced to the action of an enzyme, chlorophyllase, which is found in plants. During prolonged processes of maceration with alcohol, the chloro-

[1] Willstätter and Utzinger, *Annalen*, 1911, **382**, 129.

[*] It will be noted that at this point difficulties arise as to the exact hydrogen content of these bodies. When the lactam chlorophyll is converted into the acid chlorophyllin an atom of hydrogen is taken up by the imido group. Willstätter's formulæ take no account of this (*e.g.*, *Annalen*, 1911, **378**, 25). To avoid confusion, the present account takes as a starting-point the composition of chlorophyll-*a* as given by Willstätter in *Annalen*, 1912, **390**, 327; and it must be read accordingly.

phyllase from the plant tissues substitutes ethyl for phytyl alcohol, and "crystalline chlorophyll" is the result.[1]

As "amorphous chlorophyll" is a crude term, it may now be replaced by something more scientific, if equally cumbrous. When one carboxyl radicle of the tribasic acid termed chlorophyllin is esterified with methyl alcohol, the product is called chlorophyllide. If now a second carboxyl group in chlorophyllide be esterified with phytyl alcohol, the new substance is termed phytyl chlorophyllide. "Crystalline chlorophyll" is obviously ethyl chlorophyllide. The following formulæ * show the relations between the four compounds :—

$$C_{31}H_{30}N_3Mg\begin{cases}=NH\\ -COOH\\ -COOH\\ -COOH\end{cases}$$

Chlorophyllin.

$$C_{31}H_{30}N_3Mg\begin{cases}=NH\\ -COOH\\ -COOCH_3\\ -COOH\end{cases}$$

Chlorophyllide.

$$C_{31}H_{30}N_3Mg\begin{cases}=NH\\ -COOH\\ -COOCH_3\\ -COOC_{20}H_{39}\end{cases}$$

Phytyl chlorophyllide (Amorphous chlorophyll).

$$C_{31}H_{30}N_3Mg\begin{cases}=NH\\ -COOH\\ -COOCH_3\\ -COOC_2H_5\end{cases}$$

Ethyl chlorophyllide (Crystalline chlorophyll).

These formulæ are given with all radicles free for the sake of clearness, but actually the amino-group and the neighbouring carboxyl probably form the lactam ring immediately. The evidence on this point is given in § 7.

3. *The Structure of Phytol.*

The constitution of phytol is not yet entirely elucidated; but the available evidence[2] is sufficient to show that it has the following structure :—

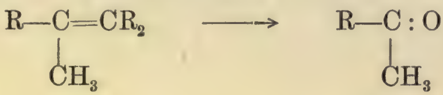
$$\begin{array}{l}C_7H_{15}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{C}}=C_4H_7-CH_2OH\end{array}$$

In the first place, when phytol is oxidized, it yields phytenic acid which has the same number of carbon atoms as phytol itself. This proves phytol to be a primary alcohol; for if it

[1] Willstätter and Stoll, *Annalen*, 1910, **378**, 18.
[2] Willstätter, Meyer, and Hüni, *Annalen*, 1910, **378**, 73.
* See footnote on p. 192.

were secondary or tertiary it would produce, on oxidation, an acid with fewer carbon atoms.

Secondly, oxidation with chromic acid breaks the chain at the fifth carbon atom counting from the hydroxyl group; and yields a methyl ketone, $C_{13}H_{27} . CO . CH_3$. This indicates that the double bond lies between the fifth carbon atom and its neighbour and, further, that that neighbour carries a methyl radicle; for the reaction is evidently the conversion of the group (I.) into the group (II.)—

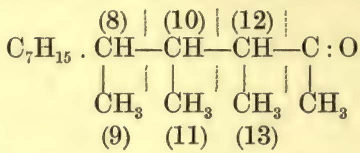


(I.) (II.)

Further oxidation gives rise in turn to a series of methyl ketones:—

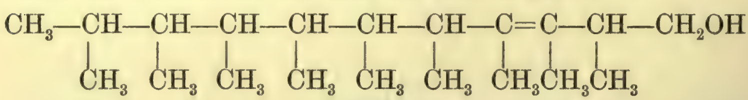
$$\overset{(12)}{C_{11}H_{23} . CO} . \overset{(13)}{CH_3} \longrightarrow \overset{(10)}{C_9H_{19} . CO} . \overset{(11)}{CH_3} \longrightarrow \overset{(8)}{C_7H_{15} . CO} . \overset{(9)}{CH_3}$$

This can only be explained by assuming that each successive carbon atom of the chain carries a methyl radicle—



The successive fragments split off during oxidation are indicated by the dotted lines.

So far the definite evidence goes. It is next assumed that the structure of the rest of the molecule is analogous to that part which has been elucidated; and on this basis the following constitution has been ascribed to phytol:—



Phytol.

A further hypothesis of Willstätter's may be noted. He points out that just as geraniol may be assumed to be built up from two molecules of isoprene and one molecule of water, so phytol might be assumed to be formed by reduction from a

compound of four isoprene molecules with one water molecule—

$$4C_5H_8 + H_2O + 3H_2 = C_{20}H_{40}O$$

It must be admitted, however, that a good deal of structure-shuffling has to be gone through in order to support this hypothesis; for at one point in the process the formation and rupture of a trimethylene ring is necessary.

4. *Chlorophyll-a and Chlorophyll-b.*

Half a century ago Stokes[1] proved that the chlorophyll occurring in plants is a mixture of two substances differing in their spectra and solubilities in certain solvents; but his paper remained almost unnoticed by later workers, and it was not until 1912 that definite chemical corroboration of his statements was obtained.[2]

The newer researches on the subject started from a different standpoint. When chlorophyll was treated with certain reagents, it was found that it yielded a mixture of two substances: phytochlorin-*e* and phytorhodin-*g*. These compounds are found to occur among the degradation products of chlorophyll in the almost constant proportion of five molecules of phytochlorin-*e* to two molecules of phytorhodin-*g*. At first sight it appears easy to account for this by assuming that the chlorophyll skeleton contains five phytochlorin nuclei and two phytorhodin nuclei; so that in its decomposition it could give rise to the products in the required proportions. This explanation breaks down at once, however, when it is shown that the molecular weights of phytochlorin and phytorhodin are each approximately the same as that of chlorophyll itself, if we deduct from the latter the molecular weight of the phytyl radicle which does not occur in either the phytochlorin or the phytorhodin molecule. Clearly, if the molecular weight of phytochlorin-*e* is nearly the same as that of the non-phytyl part of the chlorophyll molecule, there is no room in the latter substance for five phytochlorin nuclei.

Evidently only one way can be found out of the difficulty.

[1] Stokes, *Proc. Roy. Soc.*, 1864, **13**, 144; compare Tswett, *Zeit. Biol.*, 1907, 5, 6; *Ber. deutsch. bot. Ges.*, 1906, **24**, 316; 1907, **25**, 137; *Ber.*, 1908, **41**, 1352.

[2] Willstätter and Isler, *Annalen*, 1912, **390**, 269.

It is necessary to assume that chlorophyll is a mixture of two components, one of which on degradation produces phytochlorin-*e* whilst the other gives rise to phytorhodin-*g*. This view has actually been proved correct [1] by the separation of chlorophyll into two portions: chlorophyll-*a* and chlorophyll-*b*. By shaking a solution of chlorophyll in petroleum ether, with some water containing methyl alcohol, it is found that chlorophyll-*a* remains in the petroleum ether whilst the chlorophyll-*b* passes into the aqueous layer.

Chlorophyll-*a* is bluish-black in tint; contains half a molecule of water of crystallization; and gives only phytochlorin-*e* when it is decomposed. Chlorophyll-*b* is greenish-black in colour; its crystals are anhydrous; and when it is broken down it yields only phytorhodin-*g*. On analysis, chlorophyll-*a* is found to be—

$$[C_{32}H_{30}ON_4Mg](COOCH_3)(COOC_{20}H_{39}) + \tfrac{1}{2}H_2O;$$

whilst chlorophyll-*b* gives results corresponding to—

$$[C_{32}H_{28}O_2N_4Mg](COOCH_3)(COOC_{20}H_{39}).$$

5. *Phæophytins and Phæophorbides.*

When chlorophyll-*a* or chlorophyll-*b* is treated with alcoholic oxalic acid, the magnesium atom of the molecule is removed and replaced by two hydrogen atoms.* In this reaction the ester groups of the molecule are left intact. The product of the reaction is clearly the methyl-phytyl ester of the hydrogen derivative of chlorophyll. It is termed a phæophytin; and the suffix "*a*" or "*b*" is used to indicate from which of the chlorophylls it is derived.[2]

Further treatment hydrolyses away the phytyl radicle, leaving a monomethyl ester, which is called a phæophorbide. Finally, removal of the methyl radicle leaves a dibasic acid, phæophorbin. The following scheme will make the matter clear:—

[1] Willstätter and Isler, *Annalen*, 1912, **390**, 269.

[2] *Ibid.*

* The reverse change (replacement of hydrogen by magnesium) can be carried out by heating the substance with magnesium oxide and caustic potash solution or by the action of the Grignard reagent (Willstätter and Forsén, *Annalen*, 1913, **396**, 180).

$$[C_{32}H_{30}ON_4Mg]\begin{matrix}COOCH_3\\ \\ COOC_{20}H_{39}\end{matrix} \xrightarrow[+H_2]{-Mg} [C_{32}H_{32}ON_4]\begin{matrix}COOCH_3\\ \\ COOC_{20}H_{39}\end{matrix}$$

Chlorophyll-*a*. Phæophytin-*a* (Phytyl phæophorbide).

$$\xrightarrow{\text{Hydrolysis}} [C_{32}H_{32}ON_4]\begin{matrix}COOCH_3\\ \\ COOH\end{matrix} \xrightarrow{\text{Hydrolysis}} [C_{32}H_{32}ON_4]\begin{matrix}COOH\\ \\ COOH\end{matrix}$$

Phæophorbide-*a*. Phæophorbin-*a*.

As has already been remarked, the nomenclature of the chlorophyll derivatives differs from that usually employed in organic chemistry; and therefore it may render the task of the reader easier if some indication be given at this point of the relations between the various groups of compounds with which it is necessary to deal in this chapter. The two main classes are the magnesium-containing derivatives and the magnesium-free substances which are derived from the others by replacing the magnesium by two hydrogen atoms:—

Magnesium Derivatives.	Corresponding Compounds wherein the Magnesium Atom is Replaced by Two Hydrogen Atoms.
* *Chlorophyllin* $MgR(COOH)_3$	* *Phæophorbin*, *Phytochlorin* $H_2R(COOH)_3$
* *Chlorophyllide* $MgR\left\{\begin{matrix}COOCH_3\\(COOH)_2\end{matrix}\right.$	* *Phæophorbide* $H_2R\left\{\begin{matrix}COOCH_3\\(COOH)_2\end{matrix}\right.$
* *Chlorophyll* $MgR\left\{\begin{matrix}COOCH_3\\COOC_{20}H_{39}\\COOH\end{matrix}\right.$	* *Phæophytin* $H_2R\left\{\begin{matrix}COOCH_3\\COOC_{20}H_{39}\\COOH\end{matrix}\right.$
Glaucophyllin, *Rhodophyllin* *Cyanophyllin*, *Erythrophyllin* $Mg.RH(COOH)_2$	*Glaucoporphorin*, *Rhodoporphorin* *Cyanoporphorin*, *Erythroporphorin* $H_2R.H.(COOH)_2$
Pyrrophyllin, *Phyllophyllin* $Mg.RH_2(COOH)$	*Pyrroporphorin*, *Phylloporphorin* $H_2RH_2(COOH)$
Ætiophyllin $MgRH_3$	*Ætioporphorin* H_2RH_3

Inspection of the above will show that ætiophyllin and ætioporphorin are the parent substances of the two groups;

* Note that the third carboxyl group in these substances is masked by lactam formation. It has been shown free in the above formulæ merely for the sake of bringing out the analogies between the various compounds.

the other members are obtained from them by replacing hydrogen atoms by one, two, or three carboxyl radicles.

6. *The Decomposition of Chlorophyll by Alkali and by Acid.*

The action of alkali upon chlorophyll is twofold. Under certain conditions, a change in composition takes place; whilst under other conditions only rearrangements occur in the chlorophyll structure. In the present section, for the sake of clearness, the decompositions will be dealt with; and a full treatment of the intramolecular rearrangements will be deferred to the next section.

It will be remembered that when chlorophyll-*a* is submitted to the action of alkali at ordinary temperatures, the first change noted is the hydrolysis of the phytyl radicle. Thereafter, the methyl group is displaced in turn; and, finally, the salt of a tribasic acid, chlorophyllin-*a*, is produced. If, now, the temperature be raised to 140° C., carbon dioxide is split off and a dicarboxylic acid, glaucophyllin, is formed. At 165° C. in presence of alkali, this undergoes rearrangement into rhodophyllin, which is also a dibasic acid. Treated with alkali at 200° C., rhodophyllin in its turn loses carbon dioxide and yields a monocarboxylic acid, pyrrophyllin.[1]

If hot alkali be allowed to act direct upon chlorophyllide-*a*, with no previous treatment in the cold, the decomposition takes a different, but parallel course, owing to an intramolecular change occurring which produces iso-chlorophyllin-*a* instead of chlorophyllin-*a*. With alkali at 140° C. this isomeric substance yields cyanophyllin, isomeric with glaucophyllin. Cyanophyllin, when heated with alkali at 170° C., gives erythrophyllin. Finally, from erythrophyllin, alkali at 190° C. produces phyllophyllin.[2]

The following table will serve to bring out the parallelism between the various compounds formed in the latter stages of the two reactions:—

[1] Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33; and Willstätter, *Ber.*, 1914, **47**, 2854.

[2] Willstätter, *Ber.*, 1914, **47**, 2854.

Chlorophyll-*a*

$$[C_{32}H_{30}ON_4Mg]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}$$

$$\downarrow \textit{Cold alkali}$$

Chlorophyllide-*a*

$$[C_{32}H_{30}ON_4Mg]\begin{matrix}COOCH_3\\COOH\end{matrix}$$

Hot alkali. ↙	↘ *Cold alkali.*
Iso-chlorophyllin-*a* *	Chlorophyllin-*a* *
$[C_{31}H_{31}N_4Mg](COOH)_3$	$[C_{31}H_{31}N_4Mg](COOH)_3$
$-CO_2 \downarrow$ *Alkali at* 140°	$-CO_2 \downarrow$ *Alkali at* 140°
Cyanophyllin	Glaucophyllin
$[C_{31}H_{32}N_4Mg](COOH)_2$	$[C_{31}H_{32}N_4Mg](COOH)_2$
$\downarrow$ *Alkali at* 170°	$\downarrow$ *Alkali at* 165°
Erythrophyllin	Rhodophyllin
$[C_{31}H_{32}N_4Mg](COOH)_2$	$[C_{31}H_{32}N_4Mg](COOH)_2$
$-CO_2 \downarrow$ *Alkali at* 190°	$-CO_2 \downarrow$ *Alkali at* 200°
Phyllophyllin	Pyrrophyllin
$[C_{31}H_{33}N_4Mg]COOH$	$[C_{31}H_{33}N_4Mg]COOH$.

Throughout these changes the magnesium atom of chlorophyll retains its place in the molecule, as alkalis appear to have no power to displace it.

* As will be seen in the following section, chlorophyllin-*a* and iso-chlorophyllin-*a* probably contain lactam rings so that their formulæ may be written either as

$$[C_{31}H_{31}N_4Mg]\begin{matrix}COOH\\COOH\\COOH\end{matrix} \quad \text{or} \quad [C_{31}H_{29}N_3Mg]\begin{matrix}COOH\\COOH\\CO\,.\,NH-\end{matrix}$$

The action of acids upon chlorophyll, as was mentioned above, is to remove the magnesium from the molecule and replace it by two hydrogen atoms. Now it is clear that similar treatment might be given to the decomposition products of chlorophyll; and it is found that in their cases the same result follows. Thus for each magnesium-containing derivative there is a corresponding hydrogen compound.[1]

In this way we obtain from glaucophyllin the corresponding glaucoporphorin—

$$\underset{\text{Glaucophyllin.}}{\left[C_{31}H_{32}N_4Mg\right]\begin{matrix}COOH\\COOH\end{matrix}} \xrightarrow{\text{acid.}} \underset{\text{Glaucoporphorin.}}{\left[C_{31}H_{34}N_4\right]\begin{matrix}COOH\\COOH\end{matrix}}$$

and in a similar manner we get rhodoporphorin from rhodophyllin, pyrroporphorin from pyrrophyllin and phylloporphorin from phyllophyllin.*

The final stage in the decomposition of chlorophyll requires more drastic reactions.[2] If the phyllins or porphorins are heated with soda-lime in a tube they lose carbon dioxide and are converted into substances containing no carboxyl radicles. When a phyllin is used as a starting-point, the substance produced is ætiophyllin, $C_{31}H_{34}N_4Mg$; whereas when a porphorin is treated with soda-lime it yields the corresponding magnesium-free compound ætioporphorin, $C_{31}H_{36}N_4$.

The decomposition of chlorophyll-*b* follows a slightly different course, some intermediate products being missing from the series, as can be seen from the table at the end of this volume.

7. *Intramolecular Changes in the Chlorophyll Nucleus.*

When chlorophyll-*a* is treated with cold alkali, both the methyl and phytyl radicles are removed by the hydrolysis and a substance known as chlorophyllin-*a* results. On the other hand, if hot alkali solutions are employed, the end-product is an isomeric compound iso-chlorophyllin-*a*.[3] The actual progress of the reaction is marked by a peculiar colour-change. When the alkali acts on chlorophyll (or on a chlorophyllide)

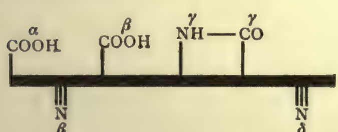
[1] Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33.
[2] Willstätter and Fischer, *Annalen*, 1913, **400**, 182.
[3] Willstätter, Fischer, and Forsén, *Annalen*, 1913, **400**, 147.
* See the table at the end of this volume.

the green tint of the substance alters to a deep brown and then, after a few minutes, the brown coloration vanishes and is replaced by the original green. The brown tint corresponds to the presence of what has been termed the "brown phase" of chlorophyll.[1]

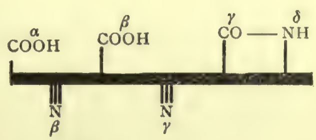
Taking these facts together, the only possible explanation of them must be found in some kind of intramolecular change occurring in the chlorophyll molecule under the action of the alkali; and Willstätter has suggested that this change involves the lactam group which was postulated as one of the radicles in the chlorophyll nucleus.[2]

He assumes that at least three of the nitrogen atoms of chlorophyll are capable of taking part in lactam rings. Then, as there are three carboxyl radicles also present in the molecule, it can be seen that a very considerable number of different lactams may be formed according to the choice which we make of the carboxyl group and the nitrogen atom which are to build up the particular lactam in question.

Let us distinguish the three carboxyl radicles from one another by the letters α, β, and γ; and let us attach the symbols, β, γ, and δ to the nitrogen atoms which Willstätter assumes to take part in the reactions. The remainder of the chlorophyll nucleus may be represented by a heavy line. On this scheme, it is clear that we might have various isomeric compounds formed, each of which would contain a different type of lactam ring. Thus the γ-nitrogen atom might be linked with the γ-carboxyl group, as in (I.); or the γ-carboxyl group might change its mode of linkage and attach itself to the δ-nitrogen atom as in (II.).



(I)



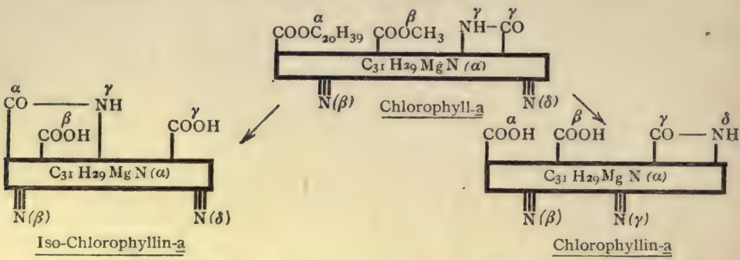
(II)

Now imagine that the compound (I.) is less stable than the compound (II.) owing to the difference in stability of the two lactam rings. It is clear that if the ring in (I.) be broken by any means it will not tend to reform itself; but that, instead,

[1] Willstätter and Utzinger, *Annalen*, 1911, **382**, 129. [2] *Ibid.*

the compound (II.) will be produced owing to the greater stability of its lactam ring.

Thus according to Willstätter's views, the formation of chlorophyllin-*a* and iso-chlorophyllin-*a* from chlorophyll may be represented in the following manner:—



This process of "allomerization," as Willstätter terms it, is obviously capable of application to the simpler chlorophyll derivatives as well as to chlorophyll itself; and when the complexity of the possible arrangements of the various carboxyl and imino radicles is taken into account it is no great wonder that three isomeric phytochlorins and an equal number of phytorhodins are known.

Both chlorophyll-*a* and chlorophyll-*b* give allomers simply on standing in alcoholic solution; which is sufficient to show how readily this intramolecular change takes place.

8. *The Magnesium Atom in the Chlorophyll Molecule.*

The part played by the magnesium atom in the structure of chlorophyll cannot be ignored if a true picture of the substance is to be obtained; yet it must be admitted that in some respects the problem which it presents is a thorny one.

From the fact that the magnesium atom remains as part of the structure of ætiophyllin, $C_{31}H_{34}N_4Mg$, it is clear that the metal must be attached to carbon or nitrogen; since all the oxygen has disappeared in the process of degradation to which the original chlorophyll has been submitted.

Now in all the magnesium-carbon compounds with which we are acquainted, the magnesium is easily removed by the action of water; it certainly cannot withstand the attack of alkali. Further, the nitrogen-magnesium bond also appears to be a weak one, if we may judge from the behaviour of mag-

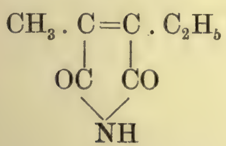
nesium methyl iodide with pyrrol.[1] Clearly the affinity which holds the magnesium atom to the chlorophyll nucleus is no ordinary bond; and we are left to conjecture its nature.

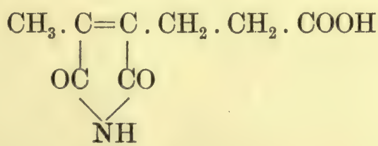
Willstätter[2] regards the metallic atom as forming a complex with the basic groups of the molecule. This question of "complex" formation is one of the debatable points in modern organic chemistry; and the fact that chlorophyll appears to be the first instance of magnesium acting in this manner will possibly not recommend the suggestion to some minds.* The problem is one which must be left to the judgment of the reader.

9. *The Structures of Ætiophyllin and Ætioporphorin.*

A consideration of the probable constitutions of the two ultimate degradation products in which the chlorophyll skeleton is retained leads us, as must frankly be admitted, into a region of almost pure hypothesis; but for the sake of completeness it is necessary to deal summarily with the subject.

The actual facts at the disposal of the investigator are very few.[3] Oxidation of phylloporphorin produces more than one molecular quantity of methyl-ethyl-maleinimide (I.) along with one molecular quantity of hæmatic acid (II.). Reduction of porphorins leads to the formation of phyllopyrrol (III.), iso-hæmopyrrol (IV.), and cryptopyrrol (V.).


(I.)

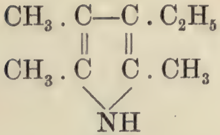

(II.)

[1] Hess and Wissing, *Ber.*, 1914, **47**, 1416.

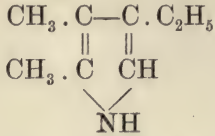
[2] Willstätter and Pfannenstiel, *Annalen*, 1908, **358**, 215; Willstätter and Fritzsche, *ibid.*, 1910, **371**, 46.

[3] Willstätter, *Ber.*, 1914, **47**, 2831.

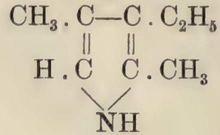
* The fact that the magnesium atom can be replaced by two hydrogen atoms without completely altering the character of the molecule makes the matter even more puzzling.



(III.)



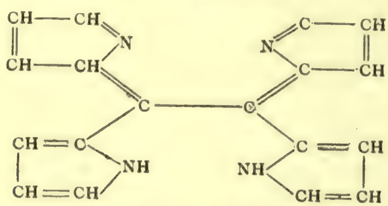
(IV.)



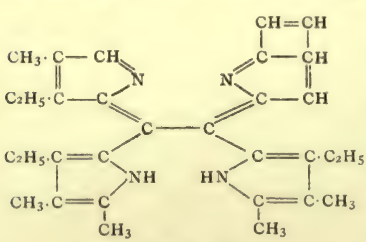
(V.)

From these disjected members it is necessary to piece together the complete skeleton of the substance.

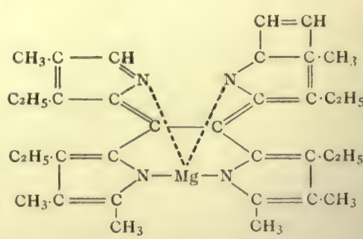
Willstätter's suggestions are as follows. From the nature of the above degradation products he assumes that the original substance must have contained four pyrrol nuclei. Now since the composition of ætioporphorin, $C_{31}H_{36}N_4$, contains a markedly low percentage of hydrogen, he concludes that the pyrrols must be so united and substituted that eight hydrogen atoms are left out as compared with the case in which the pyrrol groups are joined by single linkages. This saving of hydrogen atoms he proposes to accomplish by utilizing double bonds or calling ring formation to his assistance. Next he assumes a difference between pairs of pyrrol nuclei on the ground that two must be salt-forming radicles whilst the other two must be capable of complex formation. On this basis he suggests the following skeleton for the substance—



And from this, by substitution, he fills in the formulæ below for ætioporphorin and ætiophyllin :—



Aetioporphorin



Aetiophyllin

10. *The Relations between Chlorophyll and Hæmin.*

In the higher branches of the vegetable kingdom, chlorophyll plays a most important part in the vital economy of the organism; whilst in animals an equally essential factor is the colouring matter of the blood. The parallel functions of the two compounds suggested that some similarity in nature might be traced between chlorophyll and hæmin; and from this point of view a survey of the chlorophyll problem would be incomplete without a brief reference to the colouring material of blood.

Examination of the blood pigment shows that it is composed of two portions; an albuminous substance called globin and a non-albuminous compound named hæmatin. It is with the latter that we are here concerned.

Both chlorophyll and hæmatin are metallic derivatives, the magnesium of chlorophyll finding its analogue in the iron of hæmatin. In each case the metallic atom displays an abnormal character; and both compounds can be freed from their metallic portion by similar treatment. Finally, when analogous degradation methods are employed in the two cases, ætioporphorin is produced from both chlorophyll and hæmatin. These facts are sufficient to justify the assumption that the two substances are related to one another in a more than superficial degree.

When hæmatin is treated with hydrochloric acid it yields hæmin; and the reaction is supposed to take place by the replacement of a hydroxyl group by a chlorine atom—

$$R : Fe—OH \quad \rightarrow \quad R : Fe—Cl$$

Hæmin has recently been shown[1] to have the composition $C_{33}H_{32}O_4N_4FeCl$; which brings it into close resemblance with chlorophyllin. It will be seen that the divalent magnesium atom of chlorophyll is replaced by the divalent group: $=Fe—Cl$ in hæmin. Willstätter and Fischer[2] have brought forward a hæmin formula based to some extent upon their proposed structure for ætiophyllin. Küster,[3] on the other hand, rejects their suggestion and has put forward a formula of his own. It would require too much space to discuss the

[1] Willstätter and Fischer, *Zeitsch. physiol. Chem.*, 1913, **87**, 423.
[2] *Ibid.* [3] Küster, *Zeitsch. physiol. Chem.*, 1913, **88**, 377.

merits of either hypothesis, especially in view of the fact that both are quite possibly incorrect. In the present uncertain state of our knowledge, it is sufficient to indicate the general resemblance between chlorophyll and hæmin.

11. *Conclusion.*

As chlorophyll is a more than usually complicated subject, it seems well in this place to summarize very briefly the undisputed information which has been acquired with regard to its constitution; for without such a summary the reader may feel that he is in the position of the man who "could not see the wood for the trees".

Amorphous chlorophyll, extracted from leaves, is found to be a mixture of two compounds, chlorophyll-*a* and chlorophyll-*b*, both of which are methyl-phytyl esters. The compositions of the two compounds are:—

$$\underset{\text{Chlorophyll-}a.}{\left[C_{32}H_{30}ON_4Mg\right]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}} + \tfrac{1}{2}H_2O \quad \underset{\text{Chlorophyll-}b.}{\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}}$$

Phytyl alcohol has been shown to have the following structure:—

$$\begin{array}{l} C_7H_{15}\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}C_4H_7\text{—}CH_2OH \end{array}$$

When either of the chlorophylls is treated with acids, the magnesium atom is removed and its place is taken by two hydrogen atoms. The compounds thus formed are still methyl-phytyl esters; and they are termed phæophytins. After hydrolysis of the phytyl radicle, the residue is a methyl ester called a phæophorbide. The magnesium-free acids from which the esters are derived are named phæophorbins.

If either of the chlorophylls be acted on by cold dilute potash, the salt of a *tribasic* acid is formed, the acid itself being named a chlorophyllin. Hence, clearly, there is a third carboxyl radicle in the chlorophyll structure which is masked in some manner.

When the hydrolysis is carried out at higher temperatures in the case of chlorophyll-*a*, carbon dioxide is split off and two isomeric dicarboxylic acids, glaucophyllin and rhodophyllin,

are formed; while by the use of still higher temperatures a further loss of carbon dioxide results in the production of a monobasic acid: pyrrophyllin.

Throughout these changes the magnesium atom is retained in the molecule; but by subsequent treatment with acids each of these decomposition products loses its magnesium, which is replaced by two atoms of hydrogen. In this way from glaucophyllin a substance named glaucoporphorin is obtained; and each of the other phyllins yields the corresponding magnesium-free porphorin. The decomposition of chlorophyll-*b* proceeds in an almost exactly similar manner, though certain of the intermediate compounds are missing in its series.

When the porphorins are heated with soda-lime, the last carboxyl group of the molecule is split off; and a substance ætioporphorin, $C_{31}H_{36}N_4$, is formed. The phyllins, when subjected to the same treatment, give the corresponding magnesium derivative ætiophyllin, $C_{31}H_{34}N_4Mg$.

The action of cold alkali solutions upon either chlorophyll-*a* or chlorophyll-*b* results, as has been said, in the production of a tribasic acid. This is found to be a mixture of two acids; so that from chlorophyll-*a* we get chlorophyllin-*a* and isochlorophyllin-*a*; and from chlorophyll-*b* two other isomeric chlorophyllin-*b* compounds are produced.

Further, when chlorophyll and its derivatives are treated with alkali they exhibit a peculiar colour change, turning from green to brown and back again—the so-called "brown phase" of chlorophyll.

The magnesium atom in the chlorophyll molecule is retained with a measure of affinity different from and greater than that which we are accustomed to find in organo-magnesium derivatives.

Finally, the nature of the ultimate degradation products of chlorophyll points to the probability that the chlorophyll molecule contains four pyrrol nuclei.

The foregoing summary contains all the important *facts* which have been established with regard to the structure of chlorophyll; and we must now deal with the theories which have been advanced to account for them.

The mystery of the third carboxyl group in the chlorophyll nucleus has suggested that this third carboxyl may be masked

by lactam formation in which one of the nitrogen atoms of chlorophyll takes part. This view leads to the further hypothesis that, since there are three carboxyl groups and four nitrogen atoms present, a considerable number of possible lactam rings might be imagined, differing from one another in stability. Thus in one isomer it is assumed that the first carboxyl radicle forms a lactam with the first nitrogen atom; while in another isomer the first carboxyl reacts with, say, the second nitrogen atom to form a new lactam. On this hypothesis, the "brown phase" of chlorophyll represents the breaking of one lactam ring and the reclosing of the molecule into a more stable lactam grouping.

As to the structures proposed for ætiophyllin and ætioporphorin, their plausibility depends entirely upon the judgment of the reader; for it cannot be asserted that they have much solid basis; whilst as to the positions which the carboxyl groups of chlorophyll occupy in the ætiophyllin skeleton, not even the most random conjecture can be put forward with any justice.

CHAPTER IX.

THE ANTHOCYANINS.

1. *Introductory.*

An examination of plant pigments proves that they are, roughly, divisible into two classes. On the one hand we have the plastid pigments which are in some way intimately associated with the organized protoplasmic structure of the plant; whilst on the other hand we have soluble pigments, existing in solution in the sap of cells. These soluble pigments are termed anthocyanins.[1]

In view of the number and variety of the tints exhibited by flowers, it may appear that the term anthocyanin is a very loose one covering a multitude of colouring materials whose only relation with each other lies in the fact that they occur naturally in the sap of plants; but recent research has shown this idea to be erroneous. It seems practically established that the separate anthocyanins contain similar nuclei, no matter how much they may differ in colour from one another; and the wide variations of tint in flowers are to be ascribed to slight alterations in constitution which leave the main anthocyanin skeleton intact. Thus the anthocyanins may be regarded as a chemical class in the same way as it is customary to speak of the proteins, the carbohydrates, or the fats.

Although 250 years have passed since Boyle[2] published an investigation of the colour changes which take place when extracts from flowers are treated with acids and alkalis, it is only quite recently that much progress has been made in the

[1] A complete account of the history of the anthocyanins as well as of their botanical significance is to be found in Miss Wheldale's book, *The Anthocyanin Pigments of Plants* (1916). For briefer accounts, see Everest, *Science Progress*, 1915, IX., 597, and Willstätter, *Ber.*, 1914, **47**, 2831.

[2] Robert Boyle, *Experiments and Considerations Touching Colours*, 1664.

study of the anthocyanin group.[1] The unstable nature of the compounds and the difficulty of preparing them in a pure state militated against research in this field. It was not until 1903 that an anthocyanin was first obtained in a crystalline condition by Griffiths.[2]

The next important stage in the history of the subject is marked by Grafe's discovery[3] that certain of the anthocyanins occurred in plants in the form of glucosides.

Meanwhile, on the botanical side of the problem, a considerable amount of work had been carried out chiefly dealing with the mode of formation of the anthocyanins in plants. Miss Wheldale[4] first suggested that anthocyanins might be formed from glucosides of the flavone or xanthone series by the action of oxidases; she indicated[5] that there are a certain number of anthocyanin types which give rise to a definite series of colour varieties.[6]

Having now surveyed the outlines of the anthocyanins' history from the chemical standpoint, it will be convenient, in the remainder of this chapter, to abandon the chronological method and deal with the present-day work in an order which will render the subject more readily comprehensible.

2. *The Methods of Extracting the Pigments from Flowers.*

The choice of a suitable raw material from which to extract flower pigments is the first step which must be taken; and here two alternatives present themselves, for either fresh flowers or dried petals might be selected as the best source of the required product. The anthocyanins, under certain conditions, are unstable substances; and from this point of view it might be thought best to work up fresh flowers rather than to risk the chance of decomposition taking place during the drying process. As against this, there are certain practical arguments. In the first place, plants are in flower only during

[1] A complete bibliography of the literature is to be found in Miss Wheldale's *Anthocyanin Pigments of Plants.*

[2] Griffiths, *Chem. News*, **88**, 249; *Ber.*, 1903, **36**, 3959.

[3] Grafe, *Sitzber. k. Akad. Wien.*, 1906, **115**, I., 975; 1909, **118**, I., 1033; 1911, **120**, I., 765.

[4] Miss Wheldale, *Proc. Phil. Soc. Camb.*, 1909, **15**, 137.

[5] *Ibid.*, *Proc. Roy. Soc.*, 1909, **81**, B, 44.

[6] Nierenstein and Miss Wheldale, *Ber.*, 1911, **44**, 3487.

a short period of the year and in certain definite localities; so that the choice of fresh flowers as a source of anthocyanins would entail the necessity of carrying out the extraction of the pigment at fixed times and places, and would demand the simultaneous collection of a very large number of flowers if any great quantity of raw material were required. Secondly, in fresh flowers the plant enzymes are still active, and their influence might make itself disagreeably marked in the course of the extraction. The substitution of dried petals for fresh flowers obviates both these difficulties, but on the other hand there is the possibility of a loss of anthocyanin owing to decomposition during the process of drying. Balancing one set of disadvantages against the other, it is found in practice better to employ the dried material than to use fresh flowers; and the extraction is generally carried out by using finely ground dried petals.

The solvent chosen for the removal of the pigment from the petals of flowers or the skins of berries varies, of course, according to the nature of the anthocyanin present. In the case of the cornflower,[1] water alone suffices to dissolve the colouring material; hydrochloric acid in methyl alcohol solution is used in the cases of the rose,[2] the hollyhock,[3] the mallow,[4] the peony[5] and the bilberry;[6] dilute alcohol is employed to remove the pigments from the larkspur[7] and the scarlet pelargonium;[8] whilst acetic acid is found to be the best solvent in the cases of the grape[9] and whortleberry.[10]

After the pigment has been obtained in solution it may be purified by one of three main methods:—[11]

1. Precipitation and crystallization of the chloride.
2. Purification by suitable reagents and crystallization of the chloride.
3. Separation in the form of a picrate and subsequent conversion into the chloride.

Under the first head come such cases as the precipitation of the chloride from alcoholic solution by means of ether. Ex-

[1] Willstätter and Everest, *Annalen*, 1913, **401**, 189.
[2] Willstätter and Nolan, *ibid.*, 1915, **408**, 1.
[3] Willstätter and Martin, *ibid.*, 110.
[4] Willstätter and Mieg, *ibid.*, 122.
[5] Willstätter and Nolan, *ibid.*, 136.
[6] Willstätter and Zollinger, *ibid.*, 86.
[7] Willstätter and Mieg, *ibid.*, 61.
[8] Willstätter and Bolton, *ibid.*, 42.
[9] Willstätter and Zollinger, *ibid.*, 86.
[10] Willstätter and Mallison, *ibid.*, 15.
[11] *Ibid.*, 160.

amples of the second category are to be found in the preparation of the cornflower pigment which occurs as an alkali salt and can be purified by precipitating its aqueous solution with alcohol; and in the purification of the larkspur anthocyanin by heating it with dilute hydrochloric acid. In the picrate method the picrate is formed in the usual manner, purified, and then decomposed by a concentrated solution of hydrochloric acid in methyl alcohol.

3. *The Constitutions of Cyanin and Cyanidin.*

The pigment extracted from the cornflower is termed cyanin; and it is generally prepared in the form of its chloride, which is found to have the composition $C_{27}H_{31}O_{16}Cl$.[1] When this substance is heated for a few minutes with 20 per cent. hydrochloric acid, it is hydrolyzed, yielding two molecules of glucose and one molecule of a crystalline substance which has been named cyanidin chloride [2]—

$$\underset{\text{Cyanin chloride.}}{C_{27}H_{31}O_{16}Cl} + 2H_2O = \underset{\text{Cyanidin chloride.}}{C_{15}H_{11}O_6Cl} + \underset{\text{Glucose.}}{2C_6H_{12}O_6}$$

This reaction proves that cyanin is a diglucoside of the new body, cyanidin; * and, since glucose is colourless and cyanidin is coloured, this cyanidin forms the chromophoric portion of the pigment molecule.

The general structure of cyanidin has been established by its synthesis from quercetin,[3] and it may be well to give the complete synthetic process here, in order to show how cyanidin can actually be prepared from purely artificial materials.

In the Kostanecki synthesis [4] of quercetin (see scheme on p. 213), 2-hydroxy-4 : 6-dimethoxy-acetophenone (I.) is condensed with dimethoxyprotocatechuic aldehyde (II.) yielding 2′-hydroxy-4′ : 6′ : 3 : 4-tetramethoxychalkone (III.). On heating this for twenty-four hours with dilute hydrochloric acid, 1 : 3 : 3′ : 4-tetramethoxyflavonone (IV.) is produced. Treatment of this with amyl nitrite and hydrochloric acid converts

[1] Willstätter and Nolan, *Annalen*, 1914, **408**, 1.

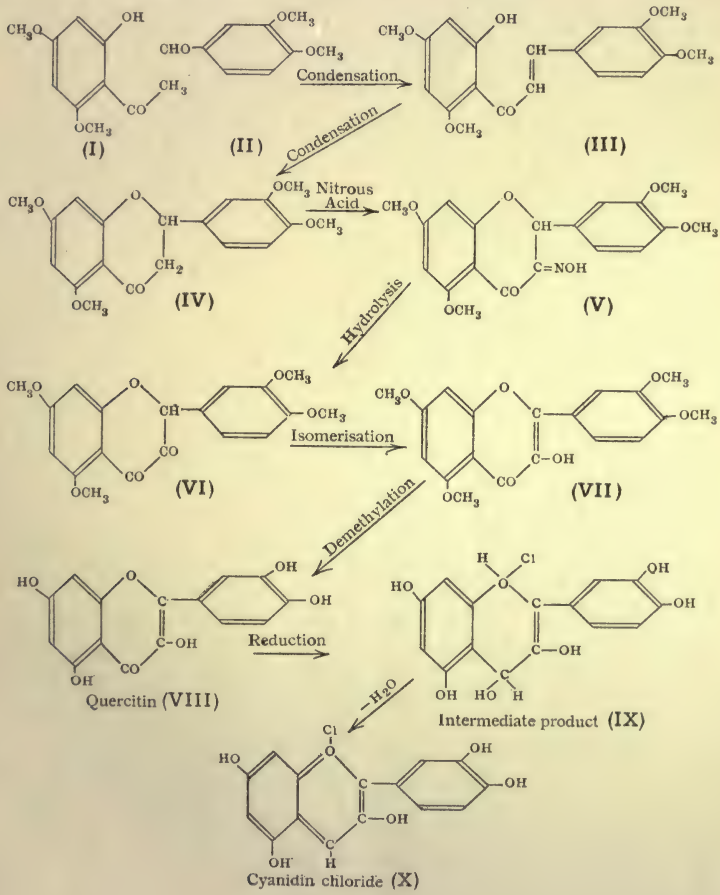
[2] Willstätter and Everest, *Annalen*, 1913, **401**, 1.

[3] Willstätter and Mallison, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 769.

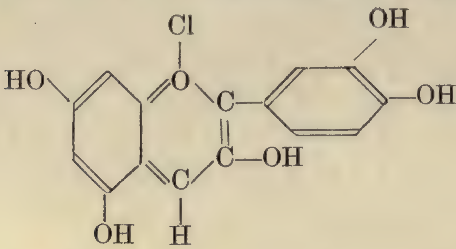
[4] Kostanecki and Tambor, *Ber.*, 1904, **37**, 793; Kostanecki, Lampe, and Tambor, *ibid.*, 1402.

* From this is derived the class-name *anthocyanidins* to indicate the non-glucosidal portions of the anthocyanins.

it into the corresponding isonitroso-compound (V.), the methylene group next the carbonyl being attacked in the usual way. Hydrolysis of the isonitroso-compound splits off hydroxylamine, leaving a ketone (VI.); after which isomerization occurs by the production of the enolic form, resulting in the production of 1 : 3 : 3′ : 4′-tetramethoxyflavanol (VII.), which on demethylation with hydriodic acid yields quercetin (VIII.). When quercetin is reduced with sodium amalgam or magnesium in alcoholic solution containing hydrochloric acid and mercury, cyanidin chloride is formed, though the yield is very small. Apparently the reaction involves the formation of an intermediate product (IX.) which then loses a molecule of water, as shown in the scheme.



An examination of the formula ascribed to cyanidin chloride



will show that it contains a peculiar heterocyclic nucleus : the pyrylium system * which was discovered by Decker and Fellenberg.[1] The reason for assuming that this grouping is present lies in the consideration of the basic nature of the cyanidin molecule. Most of the oxonium salts, those of dimethylpyrone, for example, are susceptible to hydrolysis in aqueous solution; which points to the ordinary oxonium complex being weakly basic. Pyrylium compounds, on the other hand, are much more stable in solution than the commoner oxonium derivatives; and the behaviour of the cyanin salts in this respect tends to prove that they resemble pyrylium derivatives rather than such compounds as dimethylpyrone hydrochloride. The analysis of the cyanin salts also indicates that they are not akin to the normal oxonium hydrochloride, as they contain too little hydrogen to correspond with such a structure. On these grounds the pyrylium formula has been preferred.

From these facts it is clear that the anthocyanin cyanin is a diglucoside of cyanidin, which is a pyrylium derivative of the structure shown above.

4. *The Properties of Cyanin and Cyanidin Chlorides.*

The chloride of cyanin, when prepared in the usual manner, contains two and a half molecules of water of crystallization. Under the microscope, its rhombic leaflets appear tinted between grey-violet and brownish-yellow. In dilute solutions of sulphuric acid it appears red with a tinge of violet. It is very slightly soluble in cold water, alcohol, or dilute sul-

* This is what Collie termed "oxene". See p. 245.

[1] Decker and Fellenberg, *Annalen*, 1908, **364**, 1.

phuric acid; but is easily soluble in hot water and moderately soluble in 7 per cent. acid. When sodium carbonate is added to its solution, the colour becomes first violet and then blue. Its behaviour when its aqueous solutions are diluted is peculiar. The colour of the solution weakens much more rapidly than might be anticipated and the solution may eventually become colourless. The tint of the anthocyanin can be restored either by evaporating the solution or by adding a large excess of acid. It therefore seems reasonable to suppose that the case is one of hydrolytic dissociation accompanied by intramolecular rearrangement. With ferric chloride, cyanin gives a blue tint in alcoholic solutions and a violet tinge in aqueous solutions;[1] whilst with lead acetate it gives a characteristic lead salt.[2]

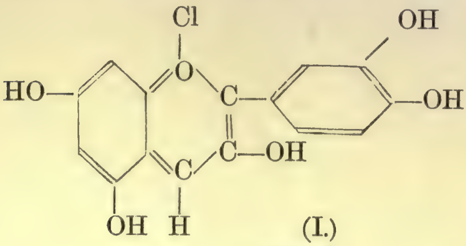
Turning now to cyanidin, it is found to crystallize with one molecule of water, which is retained with extraordinary tenacity. It is a brownish-red substance giving, when dissolved in dilute acids or alcohol, a red solution with a tinge of violet. Insoluble in water, it is readily soluble in alcohols; very slightly soluble in dilute hydrochloric acid but comparatively soluble in 7 per cent. sulphuric acid. With sodium carbonate it gives the same colour change as cyanin, turning first to blue and then to violet. The hydrolytic dissociation of cyanidin is much more marked than that of its parent anthocyanin; for when hot water is added to its alcoholic solution a violet precipitate is produced. The reaction with ferric chloride is slightly different also; for in alcohol a stable blue coloration is produced by cyanidin; whereas in aqueous alcoholic solution only an unstable violet tint is observed.[3] As in the case of cyanin, lead acetate yields a characteristic salt of cyanidin.[4]

The nature of the colourless modifications which are obtained by hydrolytic dissociation from both cyanin and cyanidin is not very clearly understood. In the case of cyanin chloride, it is found[5] that decolorization takes place when the chloride is heated for a short time in dilute alcohol at 80° C. The decolorized substance has properties resembling

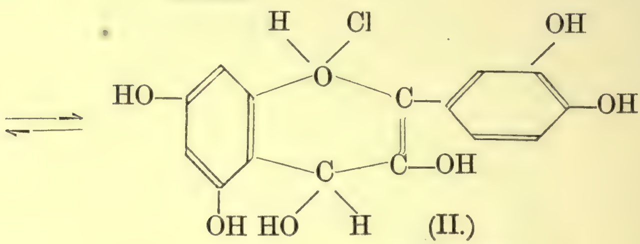
[1] Willstätter and Mieg, *Annalen*, 1915, **408**, 124.
[2] Willstätter and Everest, *Annalen*, 1913, **401**, 225.
[3] Willstätter and Mieg, *Annalen*, 1915, **408**, 125.
[4] Willstätter and Everest, *Annalen*, 1913, **401**, 229.
[5] Everest, *Proc. Roy. Soc.*, 1914, **87**, B., 444.

those of a yellow flavonol pigment; it is soluble in ether; colourless in acid solution, yellow in alkaline solution; from acid solutions it can be extracted with ether, from which it can be removed by shaking with alkali. On boiling with acids the colourless variety is reconverted into the ordinary coloured cyanidin salt.

Everest[1] suggests that cyanin chloride exists in solution as an equilibrium mixture of (I.)* and (II.), and that one set of conditions favours the stability of (I.), whilst under other conditions (II.) is the more stable form.



(I.)
Coloured.



(II.)
Colourless.

A distinction between anthocyanins and the corresponding anthocyanidins is found in the fact that amyl alcohol does not extract the former from acid solutions; but if the solution be heated so as to hydrolyze the anthocyanins to anthocyanidin, the latter passes into amyl alcohol readily.[2]

5. *The Synthesis of Pelargonidin.*

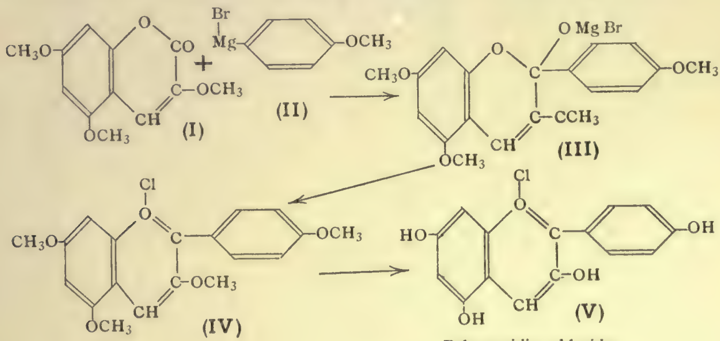
The flowers of the scarlet pelargonium are found to contain an anthocyanin which has been named pelargonin. This substance when isolated in the form of its chloride is shown to

[1] Everest, *Proc. Roy. Soc.*, 1914, **87**, B, 444.
[2] Willstätter and Everest, *Annalen*, 1913, **401**, 205.
* The glucose molecules are omitted from the formula.

have the composition $C_{27}H_{31}O_{15}Cl$, and to contain, in addition, four molecules of water of crystallization.

On hydrolysis it proves to be a glucoside, and yields two molecules of glucose and one molecule of a substance pelargonidin chloride, akin to cyanidin chloride, and having the composition $C_{15}H_{11}O_5Cl$ with one molecule of water of crystallization.

Pelargonidin[1] has recently been synthesized in the following manner: 3 : 5 : 7-trimethoxycoumarin (I.) is allowed to interact with magnesium anisyl bromide (II.). When the intermediate compound (III.) is hydrolyzed with hydrochloric acid it yields anisyltrimethoxyphenopyrylium chloride (IV.) which, after demethylation with hydriodic acid and treatment with hydrochloric acid, produces a substance (V.) indistinguishable chemically or spectroscopically from natural pelargonidin—



Pelargonidin chloride

6. *The Constitutions of Delphinin and Delphinidin.*

The anthocyanin of the larkspur is termed delphinin[2] and with it a slightly more complex field is entered. A glance at the formula of delphinin chloride, $C_{41}H_{39}O_{21}Cl$, shows that it has a molecular weight of 902 as compared with 646 for cyanin chloride; so it is evident that the former substance must contain some heavy radicle in addition to those found in cyanin or pelargonin.

Hydrolysis of delphinin proves the correctness of this. In

[1] Willstätter and Zechmeister, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 886.

[2] Willstätter and Mieg, *Annalen*, 1915, **408**, 61.

addition to the products which might be expected (glucose and delphinidin) two molecules of *p*-hydroxybenzoic acid make their appearance; so that the equation for the reaction may be written thus—

$$\underset{\text{Delphinin chloride.}}{C_{41}H_{39}O_{21}Cl} + 4H_2O = \underset{\text{Glucose.}}{2C_6H_{12}O_6} + \underset{\textit{p}\text{-Hydroxybenzoic acid.}}{2HO\,.\,C_6H_4\,.\,COOH} + \underset{\text{Delphinidin chloride.}}{C_{15}H_{11}O_7Cl}$$

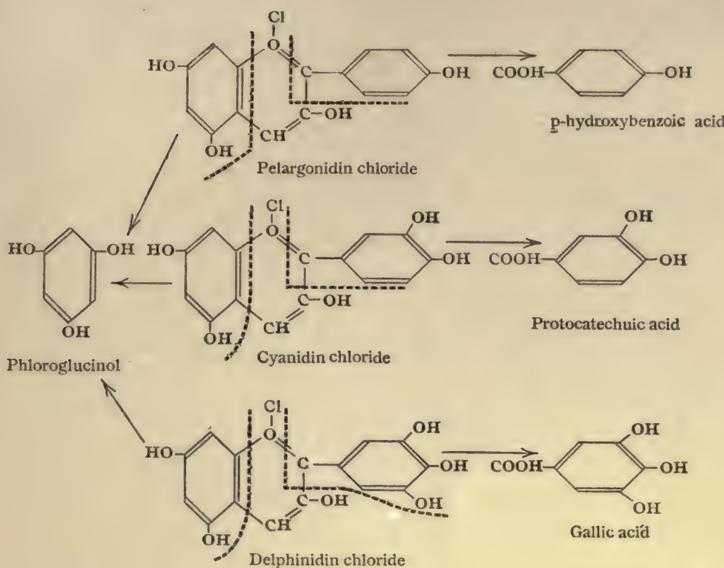
It appears from this that delphinin, like the other anthocyanins, is a glucoside; but that two of its hydroxyl radicles are esterified with *p*-hydroxybenzoic acid. Which of the hydroxyl groups are thus affected is not known definitely; but by analogy with populin (benzoylsalicin) it is assumed that the benzoylation takes place in the glucose chain and not in the delphinidin portion of the molecule.

The next stage in the deduction of delphinin's constitution is made by comparing the formulæ of pelargonidin, cyanidin, and delphinidin chlorides:—

Pelargonidin chloride	$C_{15}H_{11}O_5Cl$	or	$C_{15}H_7OCl(OH)_4$
Cyanidin chloride	$C_{15}H_{11}O_6Cl$	or	$C_{15}H_6OCl(OH)_5$
Delphinidin chloride	$C_{15}H_{11}O_7Cl$	or	$C_{15}H_5OCl(OH)_6$?

The comparison suggests that the difference between cyanidin and delphinidin may lie in the presence of an extra hydroxyl group in the delphinidin molecule.

Confirmation of this view is obtained when the results of heating the three compounds with alkali are considered. All three yield phloroglucinol; so that they contain a common grouping. In addition to the trihydric phenol, however, pelargonidin yields *p*-hydroxybenzoic acid; cyanidin produces protocatechuic acid; whilst delphinidin gives rise to gallic acid. From this it appears a reasonable deduction that the portion of the molecule which produces *p*-hydroxybenzoic acid in the case of pelargonidin is the same in nature as that which gives rise to gallic acid from delphinidin. A comparison between the two established formulæ and the one suggested for delphinidin will make the matter clear:—



7. *Other Anthocyanins.*

Mention must now be made of some other plant pigments which contain the skeletons we have already described, though the details of their structures have not yet been entirely cleared up.

Pelargonidin forms the basis of the anthocyanin of the flowers of the plant *Salvia coccinea.* This anthocyanin is called salvianin ; and on hydrolysis it yields pelargonidin, two molecules of dextrose, and a considerable quantity of malonic acid. It is therefore more complex in its structure than the usual flower pigment.[1]

In the summer aster occurs an anthocyanin, callistephin, which on hydrolysis produces pelargonidin and one molecule of dextrose.[2] The same flowers yield a second anthocyanin, asterin, which hydrolyses into cyanidin and dextrose.[3]

The anthocyanin of the winter aster is chrysanthemin, derived from dextrose and cyanidin. Cyanidin also forms the foundation for the colours of *Zinnia elegans, Gaillardia bicolor,*

[1] Willstätter and Bolton, *Annalen,* 1916, **412**, 113.

[2] Willstätter and Burdick, *Annalen,* 1916, **412**, 149.

[3] *Ibid.*

Helenium autumnale, Gladiolus Tulipa Gesneriana, Tropœolum majus, Rubes rubrum, the raspberry, and the berry of the mountain ash.[1] The cherry contains keracyanin, built up from cyanidin, dextrose, and rhamnose; whilst the sloe owes its colour to prunicyanin, which is formed from cyanidin, rhamnose, and some as yet unidentified hexose.[2] The plum also contains a cyanidin glucoside.[3]

Peonin, the anthocyanin of the peony, belongs to the cyanidin series. It is a diglucoside of peonidin, which appears to be a methyl derivative of cyanidin in which the methyl radicle replaces a hydrogen atom of one of the hydroxyl groups.[4] Another cyanidin derivative is idaein,[5] the anthocyanin of the whortleberry. It differs from the usual type of anthocyanin in that it is a galactoside and not a glucoside.

The poppy[6] contains two anthocyanins, one of them, mecocyanin, being a cyanidin derivative whilst the other resembles the glucosides of delphinidin.

Turning to delphinidin derivatives, it is found that the pansy owes its colour to the anthocyanin violanin,[7] which on hydrolysis yields delphinidin, rhamnose, and some as yet unidentified hexose, though these three products do not occur in equimolecular quantities in the reaction mixture. Monomethyl ethers of delphinidin are found in myrtillin,[8] the anthocyanin of bilberries, and petunin,[9] the anthocyanin of petunias. Dimethol ethers of delphinidin have been isolated from oenin,[10] the anthocyanin of grapes, and from malvin,[11] the anthocyanin of the wild mallow.

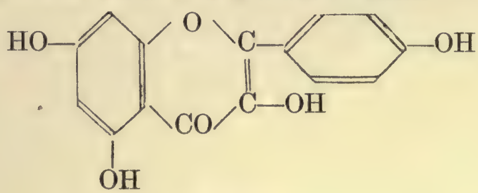
Finally, mention may be made of a glucoside ampelosin, which occurs in the wild vine. Its constitution has not yet been determined.

[1] Willstätter and Bolton, *Annalen*, 1916, **412**, 136.
[2] Willstätter and Zollinger, *Annalen*, 1916, **412**, 164.
[3] *Ibid.*
[4] Willstätter and Nolan, *Annalen*, 1915, **408**, 136.
[5] Willstätter and Mallison, *Annalen*, 1915, **408**, 15.
[6] Willstätter and Weil, *Annalen*, 1916, **412**, 231
[7] *Ibid.*, 178.
[8] Willstätter and Zollinger, *Annalen*, 1915, **408**, 83.
[9] Willstätter and Burdick, *Annalen*, 1916, **412**, 217.
[10] Willstätter and Zollinger, *Annalen*, 1915, **408**, 83.
[11] Willstätter and Mieg, *Annalen*, 1915, **408**, 122.

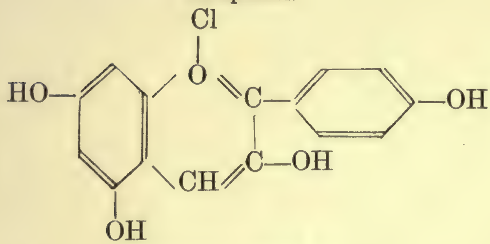
8. *The Anthocyanins and the Flavones.*

It may be of interest to point out the similarity in structure which can be traced between the flower pigments and the natural dyes occurring in plants; for the close resemblance in the skeletons of the two classes may throw light in the future upon the mode in which both types are built up within the organism. Such a similarity can hardly be regarded as due to mere chance.

Taking kampherol as a flavone representative, and comparing it with pelargonidin chloride as a typical example of the anthocyanins, it will be seen that they bear a striking resemblance to one another in general structure:—



Kampherol.



Pelargonidin chloride.

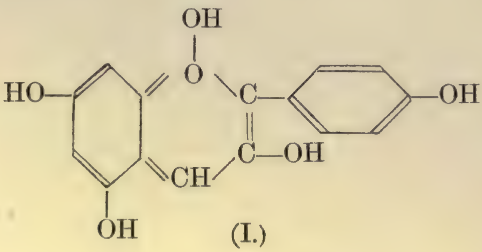
The only difference between them is to be found in the heterocyclic nucleus; the one is a true pyrone, whilst the other contains a – CH = group instead of the carbonyl radicle; and its structure is therefore more benzenoid in character. This difference is, of course, exhibited in their salts; the kampherol salts, being derived from a true pyrone, are easily hydrolyzed even in the sap of plants; whilst the salts of anthocyanins are sufficiently stable to exist without decomposition in the vegetable structure.

9. *The Origin of Colour Variation in Plants.*

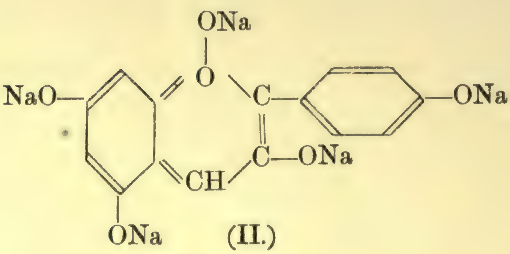
In view of the strong family resemblance between the various plant pigments, it may be interesting to indicate the

manner in which such closely related compounds might give rise to such gradations of tint as are shown in flowers.

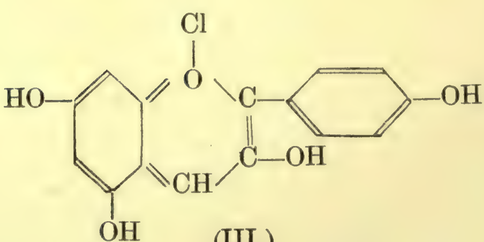
An examination of the structure of pelargonidin will show that it is capable of yielding various types of derivatives: metallic salts like (II.), oxonium salts like (III.), and internal ethers like (IV.) :—



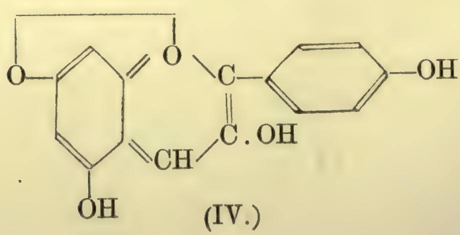
(I.)



(II.)



(III.)



(IV.)

The existence of these various types would be conditioned by the nature of the sap in the neighbourhood of the pigment; and as the sap must obviously be more highly concentrated the nearer we go to the evaporating surface of the petals, it is evident that variations in the structure of the pigment must be expected. Again, the sap in certain parts of the plant may be more alkaline than in others; and as the cyanidins are indicators, it is clear that their tint will be affected by this factor also.

CHAPTER X.

SOME THEORIES OF THE NATURAL SYNTHESES OF VITAL PRODUCTS.*

1. *Introductory.*

WHEN we survey that portion of organic chemistry which deals with compounds derived from natural sources, it is impossible to overlook the fact that, although we can synthesize many of these substances in our laboratories, the methods which we employ there differ entirely from those which are utilized in the natural production of the same substances by physiological or phytological means.

The first great difference between the lines of syntheses is found in the ranges of temperature employed in the two cases. In the plant or in the animal body, the reactions which build up extremely complicated products take place, obviously, within very narrow temperature limits; whilst in our laboratories we employ conditions varying from one another by as much as 300° C. Not only so, but we press into our service reagents of such instability and reactive power that it is impossible to conceive their coming into existence at all in the animal or vegetable kingdom.

It may be argued that this is only natural. After all, our object in laboratory practice is to obtain the best yield in the shortest time; and a resort to natural methods may be regarded with the same distaste as might be shown by a traveller from London to Inverness at the suggestion that he should tear

* When this chapter was under consideration, Professor Collie, at my request, sent me a communication embodying some of his views on the subject; and these appeared to me to necessitate the re-writing of the major part of the chapter on the basis of his notes. To avoid continual reference to this private communication and at the same time to indicate his share in the matter, I have placed a † at the beginning of each paragraph which is derived from his notes.—A. W. S.

up his first-class railway ticket and perform his journey on foot. But on the other side there is something to be said also. Very little is as yet known with regard to vital syntheses; and it is quite possible that the methods adopted by the living machine, when we come to understand them, may be simpler and more efficient than our present-day laboratory reactions. Even if this view proves to be erroneous, there can be no doubt that attempts to throw light upon plant and animal methods will broaden our outlook upon organic chemistry as a whole; for at present organic chemists, almost without exception, leave this branch of the subject severely alone.

† One reason for this abstention is perhaps to be found in the manner in which our chemical literature is compiled. In the textbooks of the subject, the naturally occurring substances are not grouped according to their place of origin but are arranged under the headings of alcohols, acids, etc., and are scattered about the literature merely to fill up gaps in long lists of artificially prepared compounds.[1] Organic chemistry of to-day is not properly organic chemistry at all, but has swollen into a chemistry of thousands of carbon compounds which do not occur in nature. Many of these synthetic compounds are the result of the immense industry of chemists who have been misled by the idea that a new compound must necessarily be interesting; and also of the very narrow outlook of certain other chemists who think that a graphic formula is the be-all and end-all of the science.

† Of course the chief reason why in textbooks we find so little information about "how" and "why" certain compounds are produced in plants and animals is because we do not know the answers to the questions involved. In the plant, for example, there appears to be no step-by-step process for making more and more complex materials, as we do in the laboratory. Carbon dioxide, water, and nitrogen, combined or otherwise, are absorbed by the green plant in sunlight. The first substances which can be isolated from the reaction products are sugars, the next ones are the highly complex starches, celluloses, and proteins. All the organic compounds

[1] Haas and Hill's *Chemistry of Plant Products* (1917) gives an excellent survey of the "organic" field, and should be consulted by anyone who desires to go further into the subject.

such as acids, esters, fats, colouring matters, and alkaloids are most probably formed by a down-grade process: a decomposition of the starches, celluloses, and proteins. The chemist in his laboratory seeks to make these compounds by syntheses from simpler bodies; the plant appears to produce them by a reverse operation from stored-up material of an extremely complex molecular structure.

† Some of these down-grade processes can be followed to a certain extent in the laboratory. Cellulose, starch, and protein can be hydrolyzed, oxidized or otherwise decomposed. But our methods, as a rule, are too violent; and the fine grades of reaction which take place slowly at ordinary temperatures in plants have, up to the present, defied imitation in the laboratory.

† Nevertheless, we must not lose sight of the fact that although natural reactions often *seem* to operate in a way quite different from laboratory reactions, yet both sets must obey the same laws. Therefore, if we find that in the synthetic processes of our laboratories certain lines are followed under conditions which could exist in plants, we are not far wrong in assuming that, in the down-grade processes of nature, the same general direction will be taken in the formation of products.

† Another point arises here. All reactions which are likely to be employed in vital syntheses are reversible; and hence if they be carried out in glass test-tubes they must come to an equilibrium point, except in those cases wherein gaseous products are formed. How, then, does the plant succeed in producing its high yields of certain substances which, in a test-tube, would be formed only in minor quantities from the same reagents? When we examine the living plant, we are at once struck by the wonderful mechanism of the natural chemical laboratory which we find there. It is a system of test-tubes made of cellulose and differing from ordinary test-tubes in that the walls are constructed from semi-permeable membranes. Each cellulose test-tube is immersed in a solution differing from that which is contained within the cellulose vessel. The membrane acts not only as a container, as the glass test-tube does, but in addition it behaves as a filter, a concentrator, or a separator. Thus during the progress of a down-

grade reaction in which a complex molecule is broken up into constituent parts, the cellulose wall permits a certain product to accumulate in one part of the plant whilst a mixture of other compounds may be withdrawn to a different region. In this way the ordinary equilibrium stage of the reaction is evaded; and much higher yields may thus be attained.

† But what starts this down-grade process? Once the plant has synthesized its starches, etc., why are these substances not stable, as they are when we place them in bottles in a chemical museum? To answer this question we must know how the plant grows; and what is meant by a living material as opposed to dead matter. The differences between the two are much too marked to allow of dispute.

† When a crystal grows in a solution, we may regard the process as the first glimmering of individual life in that particular substance. Infinitely more complex is the growth of protoplasm from carbon, hydrogen, nitrogen, and oxygen; the smallest particle of protoplasm is inconceivably greater than the atoms from which it has been built up. Still more complex is the growth of a plant from its seed. In all these cases a directive agency seems to be at work. Whether further investigation will or will not show that all these phenomena can be explained by purely chemical and physical laws, time alone can show; but it is quite certain that at present the only scientific course is to admit that we do not know. The chemical reactions which take place in the living plant are in certain respects so different from those which go on in the laboratory that we are forced to recognize the action of some subtle agency which, up to the present, we have been unable to imitate.

† Let us return to the degradation of the starches, celluloses, and proteins. The plant, under the action of sunlight, has stored these substances in its body and has grown to its full size. The directive force begins to get exhausted; the plant is growing old; most of its starches are now used up; and the celluloses and proteins are beginning to undergo more and more rapid decomposition. The down-grade process has set in with increasing velocity. The plant is still alive, but the system is losing instead of gaining energy. Fermentations have begun; but fermentations will only explain a part of

the process, for they are catalytic reactions which would, normally, reach their equilibrium stages whether the plant were young or old. The enzymes causing them are chemical reagents which enable part of the stored-up energy in the plant to be set free again; but the actual disturbance of equilibrium is due to the separation and segregation of the reaction products by the semi-permeable membranes.

It seems not impossible that the later stages in the life-history of a plant are brought about by some change in the nature of its cell-walls, akin, perhaps, to the ossification of arteries which sets in within the animal body under somewhat similar conditions. If, at this stage, the cells ceased to act as semi-permeable membranes, the whole machinery of the plant would become choked with by-products, and the natural changes which are necessary in living matter would gradually come to an end.

† During the growing phase of the plant, starches, cellulose, proteins, and enzymes are produced; but as the plant ages the growing energy lessens, the enzymes get the upper hand and prey upon the substance of the plant. They are the parasites which finally kill their parent.

† Considering the importance of the ferments in the scheme of nature, it is extraordinary to notice how very briefly they are referred to in most textbooks of organic chemistry;[1] and the textbook reflects to a great extent the outlook of the average organic chemist. It is hardly to be wondered at if the new generation of organic chemists trained by such methods becomes imbued with an almost superstitious reverence for the deluge of organic compounds which have been spawned in thousands in chemical laboratories for, apparently, no useful purpose whatever.

2. *The General Course of Vital Syntheses and Degradations.*

† When the action of the living machine is considered in its broadest aspects, there seems to be no doubt that it can be regarded as divisible into two opposed processes. In the first group come the synthetic reactions by means of which the

[1] Haas and Hill, in their *Chemistry of Plant Products*, give a very good summary of the nature of enzymes and their action in plants.

products assimilated by the plant or animal are converted into extremely complicated celluloses and proteins; whilst in the second class are placed those decompositions and changes which convert the cellulose and proteins into simpler substances. The first series of reactions are probably carried on with the absorption of external energy; the second group comprises reactions which liberate this energy once more. It may be convenient at this point to give a table indicating the course of vital action in the two cases:—

$$\left.\begin{array}{c} CO_2 + H_2O \\ \downarrow \\ \text{Sugars} \\ \downarrow \\ \text{Starches} \\ \downarrow \\ \text{Celluloses} \end{array}\right\}\text{Energy absorbed}$$

$$\begin{array}{c} \downarrow \end{array}$$

$$\left.\begin{array}{ccc} & \text{Lignocelluloses} & \\ \swarrow & \downarrow & \downarrow \\ \text{Terpenes} & \text{Benzene Derivatives} & \text{Pyrone Compounds} \end{array}\right\}\text{Energy liberated}$$

$$\left.\begin{array}{c} CO_2 + H_2O + NH_3 \\ \downarrow \\ \text{Proteins} \end{array}\right\}\text{Energy absorbed}$$

$$\begin{array}{c} \downarrow \end{array}$$

$$\left.\begin{array}{cc} & \text{Albumoses} \\ & \downarrow \\ & \text{Peptones} \\ & \downarrow \\ & \text{Polypeptides} \\ \swarrow & \downarrow \\ \text{Purines} & \text{Amino-acids} \end{array}\right\}\text{Energy liberated}$$

In the case of the cellulose synthesis, it seems evident that the reaction leads to the formation of long chains built up from sugar molecules; for hydrolysis of the cellulose yields simple carbohydrate derivatives almost unaltered. Thus in this case the reaction is quite uncomplicated and appears to be simple dehydration or polymerization.

The transformation of the celluloses into lignocelluloses

is evidently more complex, as the latter compounds appear to contain cyclic nuclei of various types; and from them the aromatic and heterocyclic substances formed in plants may be produced by a series of degradation reactions.

Turning to the proteins the same holds good in general. We have, first, the formation of simple amino-compounds which have not yet been isolated and proved to take part in the synthesis. From these, by dehydration, the proteins are formed. After this, by fermentation, we get simpler substances produced which are classed as albumoses. Further degradation yields peptones, which are closely akin to the albumoses; and finally the material breaks down into polypeptides and simple amino-acids.

3. *Possible Reactions in Vital Syntheses.*

In attempting to deduce the actual processes which lead to the formation of natural products, we are faced by two facts. In the first place, we are able to rule out as impossible such reactions as depend upon high temperatures and violent reagents; but, in the second place, we are not entitled to assume that, because up to the present we have not succeeded in making a reaction "go" at ordinary temperatures, it is therefore impossible for such a reaction to proceed effectively under these conditions. The safest course is obviously to confine ourselves as far as possible to reactions involving mild reagents and capable of proceeding economically at ordinary temperatures; though at the same time we need not exclude other reactions entirely.

Limiting ourselves thus, the choice before us is by no means so restricted as might at first be expected. Polymerization, condensation, hydrolysis, hydration and other addition reactions, dehydration, oxidation, reduction, and intramolecular change are all reactions which are known to be capable of operation at ordinary temperatures.

With regard to polymerization the data are too numerous to need reference in detail. The polymerization of aldehydes, the production of truxillic acid from cinnamic acid under the action of light, the conversion of ethylene into higher hydro-

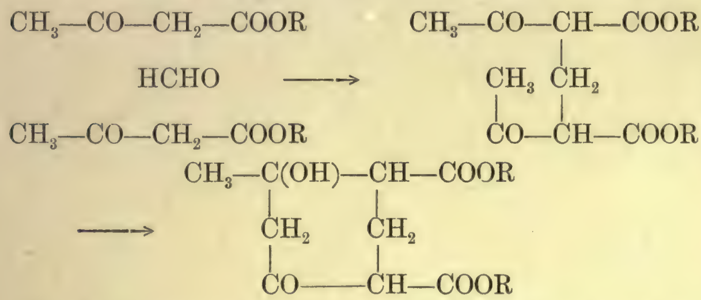
carbons and the synthesis of rubber from isoprene are too well known to render it necessary to discuss them.

When we come to condensation the matter demands a more careful scrutiny, for various types of reaction are involved, each of which has its particular application to the problem before us.[1]

The aldol condensation[2] can be carried out with the help of traces of foreign materials; and it is noteworthy that among these catalysts are to be found salts such as the acetates, carbonates, and bicarbonates of the alkalis, all of which might be found in the saps of plants.* Now the aldol condensation not only provides a means whereby carbon chains may be formed from shorter groups—

$$CH_3.CHO + CH_3.CHO = CH_3—CH(OH)—CH_2—CHO$$

but in addition it also gives rise to carbocyclic derivatives—[3]



The benzoin condensation might also be reckoned as a probable vital reaction, for, although it is usual to employ heat in the laboratory, it seems evident that this condensation proceeds at ordinary temperatures at a slower rate.

The second class of condensation under consideration includes those reactions in which ammonia molecules or their substitution products take part. Of these, apart from amide formation, the most important is the production of amino alcohols from aldehydes:—

$$R—CH:O + NH_3 = R—CH(OH)—NH_2$$

[1] See Baeyer, *Ber.*, 1870, **3**, 63.

[2] See Robinson's suggestions on this point (*Trans.*, 1917, **111**, 876); compare Raper, *Trans.*, 1907, **91**, 1831.

[3] Rabe, *Annalen*, 1908, **360**, 265.

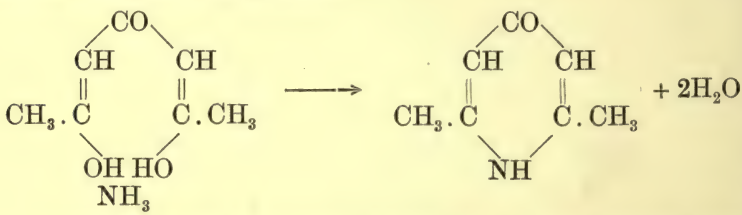
* The actual catalyst may be the hydroxyl ion.

An intramolecular application of this reaction, in which an amino-aldehyde is employed, leads to ring-formation and the production of an amino-alcohol of the following type :—

And, as Robinson[1] has shown, these amino-alcohols react readily in aqueous solutions with ketones, producing new derivatives by the elimination of water :—

$$\begin{array}{l} -\mathrm{CH.OH} \\ \;| \\ -\mathrm{N.CH_3}\end{array} \quad + \quad \mathrm{CH_3.CO.CH_3} \quad = \quad \begin{array}{l} -\mathrm{CH.CH_2.CO.CH_3} \\ \;| \\ -\mathrm{N.CH_3}\end{array}$$

Different in nature is the ring-formation produced when such substances as diacetylacetone are treated with ammonia.[2] Here one molecule of ammonia interacts simultaneously with two hydroxyl radicles—the ketone enolizing—in order to produce a derivative of pyridine—



Turning to the question of hydrolysis, it is unnecessary to dwell at length upon the ordinary reactions. Attention must be drawn, however, to the fact that the same reagents may produce different end-products according to the conditions employed. Thus acetoacetic ester derivatives may yield either a ketone or an acid in addition to acetic acid, in the ordinary acetoacetic ester synthesis.

The most important reagents in this field, however, are the enzymes; and it may be worth while to deal with their action in more detail. For the hydrolysis of the proteins, two classes

[1] Robinson, *Trans.*, 1917, **111**, 876.

[2] Collie, *Trans.*, 1907, **91**, 1806.

of enzyme are known, which are termed proteolytic. The pepsin group attack albumins only in weak acid solutions, converting them into albumoses and peptones, which are soluble albuminous compounds of complicated structure. The trypsin group, on the other hand, act only in neutral or weakly alkaline solution. A third class of enzymes, the labenzymes, have the faculty of coagulating protein compounds and are therefore termed coagulating enzymes. To some extent a fourth type of enzyme might be included in this section, since its action resembles those of the proteolytic class in so far that it depends upon the hydrolysis of the amide group. This last type has the faculty of breaking down urea and uric acid derivatives. The lipolytic enzymes are utilized to break down fats, from which they liberate glycerine. They appear to react best in acid solution.

Several enzymes are known which can be employed to hydrolyze such materials as starch; and the progress of the hydrolysis depends upon the enzyme chosen. Thus when diastase acts upon starch it converts it into soluble material and breaks it down eventually to simple carbohydrates, the end-product being maltose, $C_{12}H_{22}O_{11}$. The application of maltase carries the process a stage further, two molecules of glucose being formed. Cane-sugar is broken down by invertase to glucose and fructose.

In all these cases, of course, the enzyme acts merely as a catalytic agent and has no influence upon the equilibrium point. Thus, as has been mentioned in a previous chapter, chlorophyllase may be employed either to hydrolyze a phytyl ester or to replace the phytyl radicle by an ethyl group.

Under the head of addition reactions it is only necessary to mention one or two processes. Among the unsaturated compounds, and especially in the terpene group, water can be added on to double bonds at ordinary temperatures when acids are present.[1] Apparently the reaction takes place in two stages: a molecule of acid first attaching itself to the double linkage in order to form an ester which is then hydrolyzed, leaving an alcohol.

Under ordinary conditions also, ammonia has the faculty

[1] Wallach, *Annalen*, 1908, **360**, 102.

of attacking certain ethylenic linkages. Thus mesityl oxide takes up a molecule of ammonia to form diacetonamine—

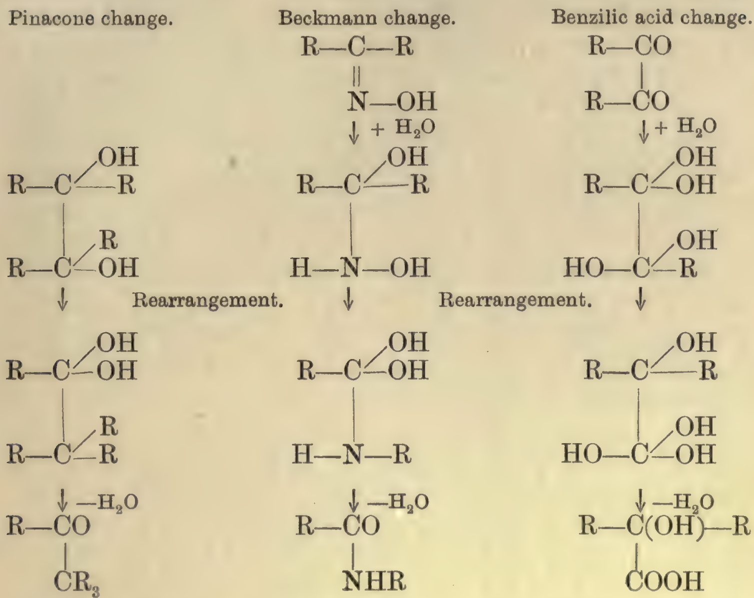
$$(CH_3)_2C : CH . CO . CH_3 + NH_3 = (CH_3)_2C(NH_2) . CH_2 . CO.CH_3.$$

Dehydration is a reaction capable of almost endless applications in the field of vital chemistry. Saturated compounds may be converted into unsaturated derivatives; carbon chains may be formed, as in the mesityl oxide and phorone syntheses; benzene derivatives and heterocyclic substances such as pyrones can be prepared without exceeding ordinary temperatures. Indeed it seems probable, though not yet proved, that a large proportion of vital syntheses depend upon successive dehydrations and rehydrations, by means of which the structure of the molecule can be altered.

As to oxidation and reduction, no doubt can be entertained as to the prominent part taken by them in vital reactions. As far as oxidation goes, we are acquainted with numerous enzymes (oxidases) which act as agents in the reactions of living tissue; and though the nature of the corresponding reducing enzymes, the reductases, has not been fully studied, there seems to be no question about their existence. Apart from enzyme action, numerous cases of spontaneous oxidation are known to the organic chemist, such as the formation of indigo from indoxyl and the production of oxyhæmoglobin from hæmoglobin.

Intramolecular change is a branch of the subject which it is hardly necessary to treat in detail; but one or two cases may be mentioned, since they may serve to throw light upon vital reactions. The most important of all is the keto-enol rearrangement; but this will be fully described in a later section.

Three isomeric changes may be grouped here together for convenience, as there appears to be a certain parallelism between them: the pinacone change, the Beckmann rearrangement, and the benzilic acid change. All three may be brought into line if it be assumed that an addition compound is formed with another reagent, taken here as water for the sake of simplicity:—



In a previous chapter we have already encountered some examples of an intramolecular rearrangement which is of the greatest importance from the point of view of natural terpene syntheses: the formation of cyclic compounds from open-chain di-olefinic derivatives. The cases of citronellal and iso-pulegol (p. 93); rhodinal and menthone (p. 98); citral and cyclo-citral (p. 100); and the conversion of geraniol, nerol, and linalool into terpineol (p. 103), are examples of the type to which we refer. These changes take place either spontaneously or under the influence of alkali or acid; and it seems not improbable that some such rearrangement leads to the production of terpenes in nature.

Among natural products, methylamine derivatives occur; and it appears probable that these are formed by the action of formaldehyde:—

$$2NH_3 + 3CH_2O = 2NH_2 . CH_3 + CO_2 + H_2O.$$

In laboratory practice the reaction takes place even at the temperature of a water-bath; so that it evidently can be carried out, though slowly, under ordinary conditions.

Photochemical effects must, of course, play a very striking

part in vital processes, especially in the vegetable kingdom. Of these, the most important from the theoretical standpoint is the discovery by Cotton [1] that the dextro and lævo forms of tartaric acid absorb *d*-circularly polarized light to different extents; which implies that such light will decompose them at different rates. Now since light is circularly polarized by the surface of the sea, we have a natural method whereby the production of unequal quantities of asymmetric material can be attained; and once the balance between the two isomers is thus disturbed, the general production of optically active compounds becomes possible. It may be that these experiments indicate the manner in which optically active substances first made their appearance on the earth's surface.

4. *The Production of Carbohydrates.*

In searching for the reservoirs from which plants draw their supplies of carbon wherewith to build up their tissues, we are limited by the fact that plant nourishment can take place through only two channels, the roots and the leaves. As far as the supply of carbon is concerned, it may at once be granted that the roots play no preponderant part. Plants can be forced to grow under conditions which preclude the possibility of any great supply of carbon through the root; and yet the organism seems to suffer nothing by this source of material being cut off. We are, therefore, thrown back upon the leaves as the essential agents in carbon assimilation.

The source from which leaves can obtain carbon compounds is obvious: the carbon dioxide of the air suffices to furnish all the carbon which the plant requires for its growth; and it only remains to consider how this is utilized by the organism.

Strangely enough, the next stage in the process is one which has given rise to most controversy.[2] It seems not improbable that the reaction takes the following form:—

$$H_2CO_3 + 2H_2O \rightleftharpoons H.CHO + 2H_2O_2$$

If, now, an enzyme be present which has the power of decom-

[1] Cotton, *Ann. Chim. Phys.*, 1896, VII., **8**, 373.

[2] See Jörgensen and Stiles, *Carbon Assimilation;* Meldola, Presidential Address, *Trans.*, 1906, **89**, 745, and also Haas and Hill, *The Chemistry of Plant Products*, p. 154 ff.

posing hydrogen peroxide,[1] there will be a continual progress from left to right of the equation, with a steady accumulation of formaldehyde in the leaf.[2] The energy required to effect this reaction must originally be drawn from solar radiation; but the immediate cause of the transformation may be due to electrical conditions on the leaf surface.[3]

Assuming that formaldehyde is thus formed, clearly it does not remain unaltered; for it was only with considerable difficulty that the presence of this substance in plant leaves was determined.[4] Evidently we are led to assume, further, that the formaldehyde is changed almost immediately into some other substance; and the experiments of Loew,[5] Fischer and Passmore [6] have shown that in presence of calcium hydrate a dilute solution of formaldehyde can be polymerized direct to racemic fructose. It seems very doubtful, however, if this simple process represents what occurs in the plant; for the sugars obtained by phytological methods are optically active, so that an asymmetric agent must make its appearance at some stage or other during their synthesis. Two alternative solutions of this problem may be considered. In the first place the agent which stimulates the polymerization of the sugar may be itself asymmetrical (an enzyme); and thus one enantiomorph may be formed in greater quantity than the other: or possibly the racemic sugar is produced by direct methods and is then acted upon by a selective enzyme such as are common in plants, with the result that one antipode is more rapidly decomposed than the other. In either way a preponderance of one active form would result. It must be frankly admitted that even in this simple problem we can only say that we do not know the true solution.

With the production of sugars of the hexose type, however, the main difficulties are ended, for by the action of enzymes these can be converted into much more complex materials, the polysaccharides;[7] and even higher complexes such as dextrin can be produced from the hexoses by catalytic means. As to the further stages by which cellulose and its analogues

[1] Loew, *Ber.*, 1902, **35**, 2487.

[2] See Gibson, *Ann. of Botany*, 1908, **22**, 117. [3] *Ibid.*

[4] *Ibid.* [5] Loew, *J. pr. chem.*, 1886, **33**, 321.

[6] Fischer and Passmore, *Ber.*, 1889, **22**, 359.

[7] Hill, *Trans.*, 1898, **73**, 634; see also Bayliss, *The Nature of Enzyme Action*.

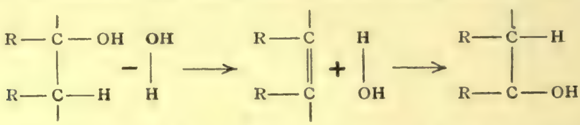
are formed, we can only admit our ignorance; though the fact that these substances can be reduced to simpler materials by catalytic action certainly suggests that they are probably built up by a similar process.

5. *Collie's Theory of Enzyme Action.*

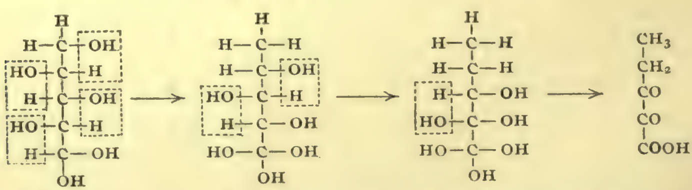
† During the break-down of certain carbohydrate derivatives under the action of enzymes, an important step in the reaction is evidently the accumulation of hydrogen atoms at one end of the chain and the gathering of oxygen atoms at another point. Only on this assumption can we explain the conversion of the radicle (I.) into the grouping (II.) which evidently takes place during alcoholic fermentation:—

$$\underset{\text{(I.)}}{CH_2OH\text{—}CH\,.\,OH\text{—}} \qquad \underset{\text{(II.)}}{CH_3\text{—}CH_2\text{—}}$$

Now if the sugar molecule be regarded as being built up from a chain of carbon atoms united with water molecules, such a transformation can readily be represented by a mere change in orientation of the hydrogen and hydroxyl radicles, which might be produced by dehydration and rehydration:—



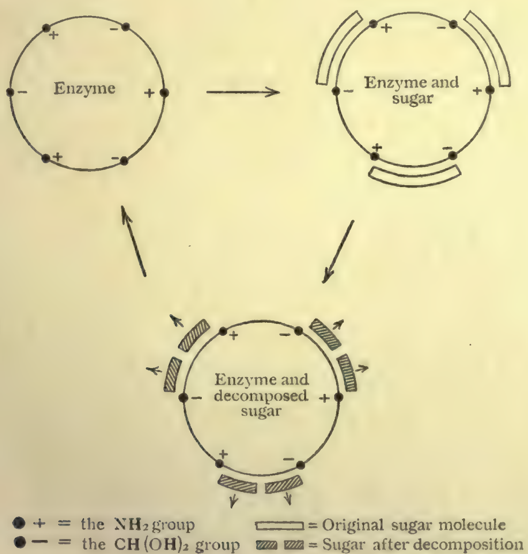
† In the case of a pentose, distinguishing the inverting groups by the dotted lines, we should get the following picture:—



† Take the case of a hexose as an illustration of the next step in the argument. At one end of the chain is the weakly basic hydroxyl group, whilst at the other end lies the aldehyde radicle, which, in its ortho-form, is weakly acidic. It is therefore reasonable to assume that the main chain of the sugar is subjected to electrical strain. Now if this electrical condition can be interfered with, changes might be expected to occur in

the molecule; and it is possible that the enzymes work in this manner. The enzyme molecule is probably built up from amino-acids somewhat in the same manner as a protein; so that it contains, like the sugar, a basic group (—NH_2) and an acidic radicle (—COOH). From what we know of their molecular complexity, the enzyme molecules must be immensely greater than the molecules of simple carbohydrates; and it is therefore probable that one molecule of enzyme may react simultaneously with hundreds of carbohydrate molecules. The basic and acidic groups of the sugar will come into contact with the acidic and basic portions of the enzyme *provided that these groups occupy suitable positions in space;** the system is then short-circuited; and what might be termed "molecular electrolysis" results; the energy of the sugar molecule is set free as heat; and, by the rearrangement of the hydrogen and hydroxyl groups of the sugar, new compounds are formed which are no longer capable of combining with the amphoteric enzyme. The latter may then be recharged by induction or by the presence of ions in the solution, as is the case with many colloids.

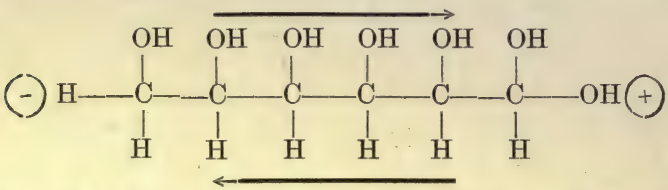
The following diagram represents the various steps in the process:—



* This serves to explain the selective power of enzymes.

In its elements the Collie theory bears a strong resemblance to Ehrlich's side-chain theory of toxins and anti-toxins, the two groups at the points attacked being analogous to Ehrlich's receptors, whilst the corresponding points in the enzyme are akin to Ehrlich's haptophore groups.

† Another possibility must not be left out of account. When we examine the structural formula of a sugar in its ortho-form the similarity between it and one of the usual diagrams to illustrate electrolysis strikes the eye at once—



Now if we imagine a pair of terminals inserted in the molecule as shown by the + and − signs, it is clear that the hydrogen atoms would be drawn to the left, whilst the hydroxyl groups would move to the right. This would give us the same accumulation of hydrogen atoms at one end and hydroxyl groups at the other. Collie's conception of the action of enzymes allows us to picture the necessary electrical terminal inserted into the molecular structure of the sugar; and it may be noted that these terminals do not necessarily attack the two ends of the chain; they might quite as easily be supposed to be inserted at any point in the molecular structure which is spatially suitable for their entry; and in this way the selective action of different enzymes may be accounted for.

6. *A Dynamic Formula for the Sugars.*

One reaction which distinguishes the sugars from almost all other compounds is their dehydration. The ease with which they split off water, leaving carbon behind, is one of their most marked characteristics; and it appears that less attention has been paid to the matter than might be profitable.

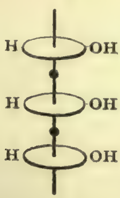
† On the basis of this reaction, a new way of regarding the sugar molecule has been proposed by Collie. Let us assume that the carbohydrate molecule is built up from a straight chain of carbon atoms combined with water molecules, thus:—

$$\begin{array}{cccc} —C— & —C— & —C— & —C— \\ (H_2O) & (H_2O) & (H_2O) & (H_2O) \end{array}$$

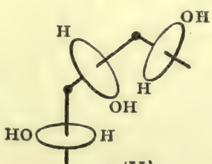
Assume, further, that these water molecules envelop the carbon atoms and *that the three atoms of the water molecule rotate round the carbon atom to which they are related.** If this rotation were entirely stopped, we should get the state of affairs represented by the usual graphic formulæ for the sugars, each hydrogen and hydroxyl group taking up its favoured position with regard to the rest of the chain. The rotation of the water molecules might, of course, be either right or left-handed.

† Now since atoms are electrical systems, this spinning of the water molecules about the carbon atoms would have the same effect as placing the carbon chain in a magnetic field; and hence on this assumption it is possible to explain the optical rotatory power of the sugars.

† The energy put into the system by sunlight would be converted into *the increased rotational energy* of the water-atoms round the carbon atoms. The action of enzymes might be supposed to be a braking effect which would tend to slow up the rotational energy and reduce the molecule to a condition represented by the ordinary static formula. When the water molecules are at their highest rotational velocity, the system would tend to bring the axes of rotation parallel, as in (I.); but when the braking effect came in there would be more tendency to librate and the system would approach the position (II.):—



(I)



(II)

Under such conditions the hydrogen and hydroxyl groups would, at certain points in their orbits, come more or less

* If the reader will clear his mind of the antiquated conception of directed valency he will have no difficulty in seeing that this idea in no way contravenes any fundamental chemical postulate.

close together, when either water could be eliminated from the system or the hydrogen of one carbon might exchange places with the hydroxyl group of the next carbon atom—

$$-CH.OH-CH.OH- \begin{array}{l} \nearrow -CH{=}C(OH)- \\ \searrow -CH_2-C(OH)_2- \end{array}$$

† As can be seen by working out the problem, it is possible to pass from a right-handed spin through the symmetrical keto-methylene grouping to a final phase in which a left-handed spin exists; so that the theory covers the case of racemization satisfactorily and also such cases as the production of lævorotatory lævulose from dextrorotatory glucose via the osazone.

7. *The Polyketides.*

As will be seen in later sections of this chapter, substances containing the keto-methylene grouping, $-CH_2 . CO-$, or its tautomeric form, $= CH . C(OH)-$, play a large part in some natural processes; and it is therefore desirable to have some general term to cover the class of compounds which contain linked keto-methylene chains. Collie[1] proposes to name *polyketides*[2] those compounds which may be regarded as built up by the polymerization of keten and the subsequent addition of a molecule of water—

$H.(CH_2CO).OH$	$H.(CH_2CO)_2.OH$	$H.(CH_2CO)_3.OH$
A monoketide (Acetic acid).	A diketide (Acetoacetic acid).	A triketide (Triacetic acid).

The members of the polyketide series are marked by two characteristics: their extreme sensitiveness to slight variations in the concentration of the reagents used upon them; and the readiness with which they undergo intramolecular change. It is unnecessary to multiply examples of their behaviour, but several typical ones must be given to show the ease with which polyketides or their derivatives can be converted into members of aliphatic, aromatic, and heterocyclic groups.

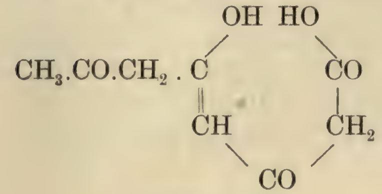
Let us take as our starting-point tetracetic acid:—

$$CH_3 . CO . CH_2 . CO . CH_2 . CO . CH_2 . COOH$$

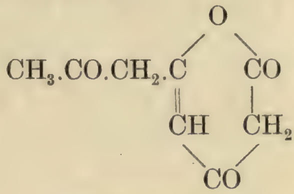
[1] Collie, *Proc.*, 1907, **23**, 230.

[2] For a general account of polyketide reactions, see Collie, *Trans.*, 1907, **91**, 1806.

This substance does not exist in the free state, but loses water at once, giving a ring compound, dehydracetic acid:—

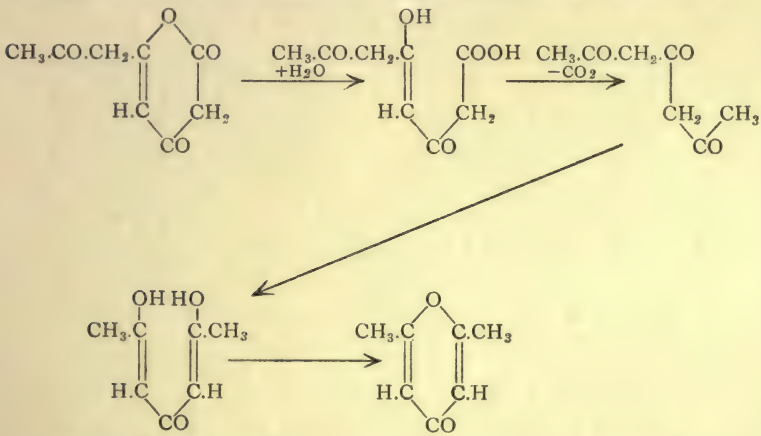


Tetracetic acid
(Enolic form).



Dehydracetic acid
(Tetracetic lactone).

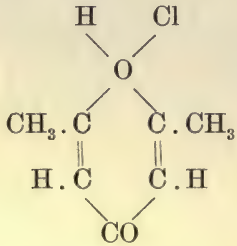
Dehydracetic acid, when heated with mineral acids, gives rise to salts of dimethyl-pyrone. The first stage in the reaction is the formation of tetracetic acid, which then loses a molecule of carbon dioxide from its carboxyl radicle; diacetyl-acetone is thus produced, which enolizes in a new position; finally, water is eliminated and dimethyl-pyrone remains:—



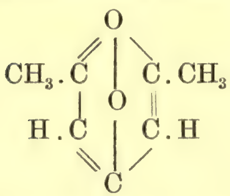
When the dimethyl-pyrone thus obtained is analysed, however, it is found to have the composition $C_7H_9O_2Cl$, which corresponds to a compound of one molecule of dimethyl-pyrone with one molecule of hydrochloric acid. The substance is not a chlorine-substituted pyrone derivative, but behaves exactly like the hydrochloride of an organic base. Collie and Tickle,[1] who were the discoverers of this class of substance, prepared a series of compounds of dimethyl-pyrone with many of the common acids, both organic and inorganic, as well as metallic

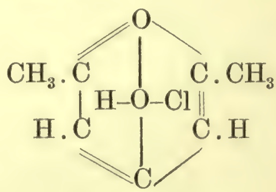
[1] Collie and Tickle, *Trans. Chem. Soc.*, 1899, **75**, 710.

double salts; and from a study of their properties drew the conclusion that the oxygen atom which forms the bridge in the pyrone nucleus has basic properties akin to those of a tertiary nitrogen atom. Thus, just as tertiary amines form ammonium salts, divalent oxygen compounds may unite with acids to form "*oxonium salts*". The compound of dimethyl-pyrone with hydrochloric acid would on this hypothesis be represented by the formula—



Though dimethyl-pyrone contains a carbonyl group, it does not react with either hydroxylamine or phenylhydrazine. This peculiar behaviour has led Collie[1] to put forward the view that not one but both the oxygen atoms in the pyrone nucleus are quadrivalent in the oxonium salts; while in the base itself one oxygen atom is supposed to be always quadrivalent. On this view the formulæ of dimethyl-pyrone and its hydrochloride would be written thus—



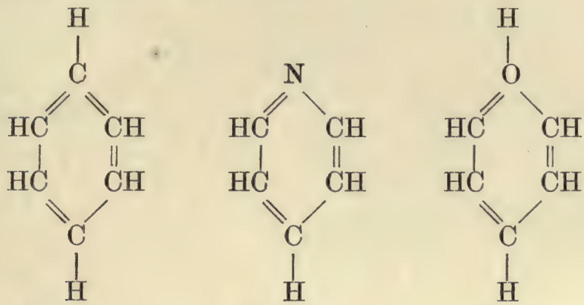


This view of the pyrone structure is supported to a certain extent by an examination of the refractive indices of pyrone derivatives which has been carried out by Miss Homfray.[2] In both of the above formulæ the peculiar resemblance to the benzenoid type is manifest, and Collie has been led to suggest that the root-substance of the pyrone class has a structure

[1] Collie, *Trans. Chem. Soc.*, 1904, **85**, 971; *cf.* Willstätter and Pummerer, *Ber.*, 1904, 3733; 1905, **38**, 1461.

[2] Homfray, *Trans. Chem. Soc.*, 1905, **87**, 1443.

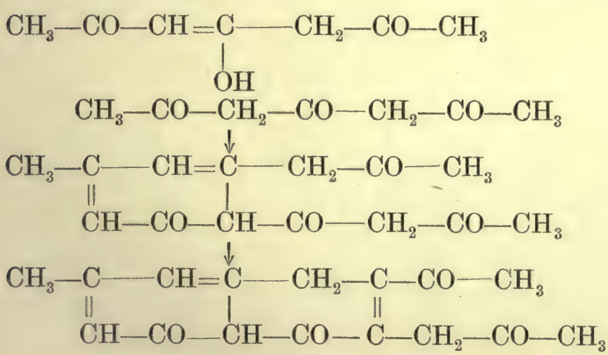
which resembles that of pyridine. To this hypothetical compound he has given the name "*oxene*,"[1] as it is the oxygen analogue of benzene and pyridine—



Benzene. Pyridine. Oxene.

Dimethyl-pyrone, under the action of alkali, yields salts of an enolic form of diacetyl-acetone, from which diacetyl-acetone itself can be obtained by adding acid.

This tetraketide derivative, diacetyl-acetone, shows a most extraordinary series of changes. On standing in a desiccator, it loses water and is reconverted into dimethyl-pyrone; with ammonia it yields a pyridine derivative, lutidone; in very weak alkaline solutions at ordinary temperatures it produces a benzene derivative which, in presence of very slightly stronger alkali, changes to a naphthalene compound:—



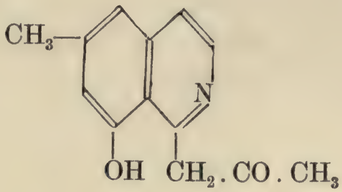
Diacetyl-acetone.

Benzene derivative (Ketonic form).

Naphthalene derivative (Diketonic form)

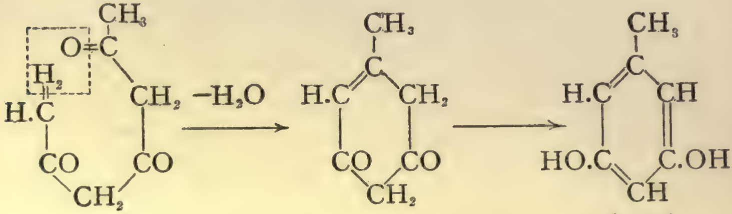
By the action of ammonia on the benzene derivative, an isoquinoline compound—

[1] Collie, *Trans. Chem. Soc.*, 1904, **85**, 971.



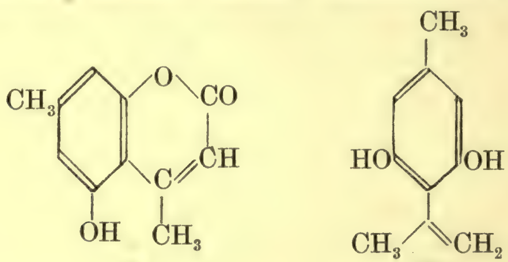
is formed.

Returning to the dehydration of diacetyl-acetone, the use of acid reagents produces another benzene derivative, orcinol—



Orcinol

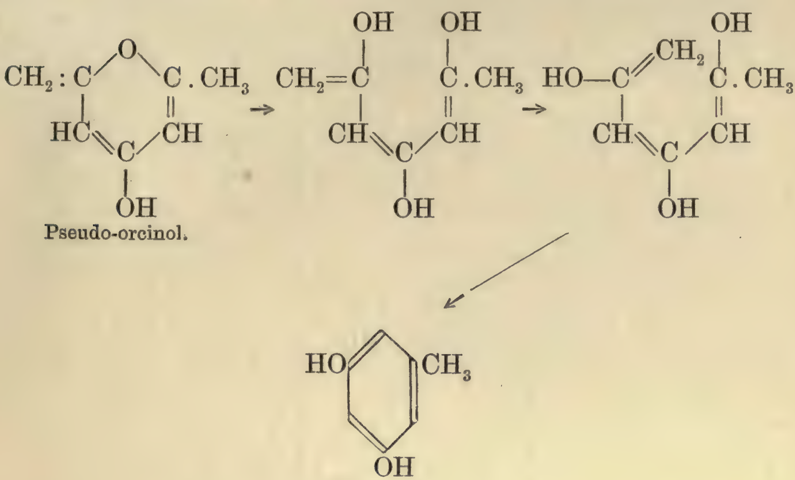
Further results are obtained by condensing the polyketide orcinol with acetoacetic ester. The reaction product, after hydrolysis, is found to be dimethyl-umbelliferone (I.)—



(I.) (II.)

and when this compound is treated with alkali and heated, it undergoes hydration and loss of carbon dioxide with the formation of a thymol derivative (II.). Orcinol also condenses with the polyketide derivative acetylacetone, yielding a benz-pyrene compound, the formula of which is given on p. 248.

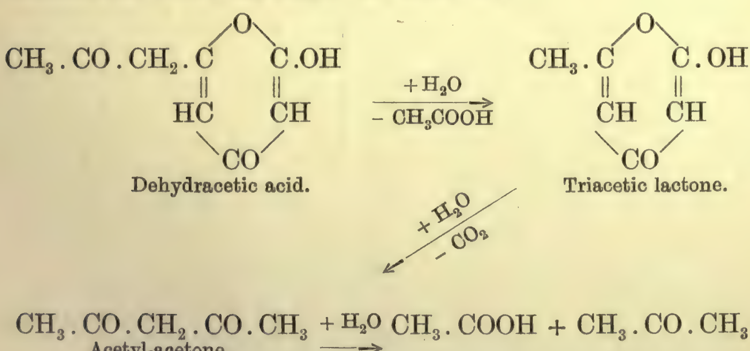
An interesting compound, pseudo-orcinol, bridging the gap between the pyrone and benzene series, was discovered by Collie and Stewart. As can be seen from its formula, the wandering of a hydrogen atom will convert it into dimethyl pyrone; whilst hydration, followed by rearrangement and de-hydration, yields orcinol. In practice, acid solutions convert it into dimethyl-pyrone, whilst alkali changes it to orcinol—



Pseudo-orcinol. Orcinol.

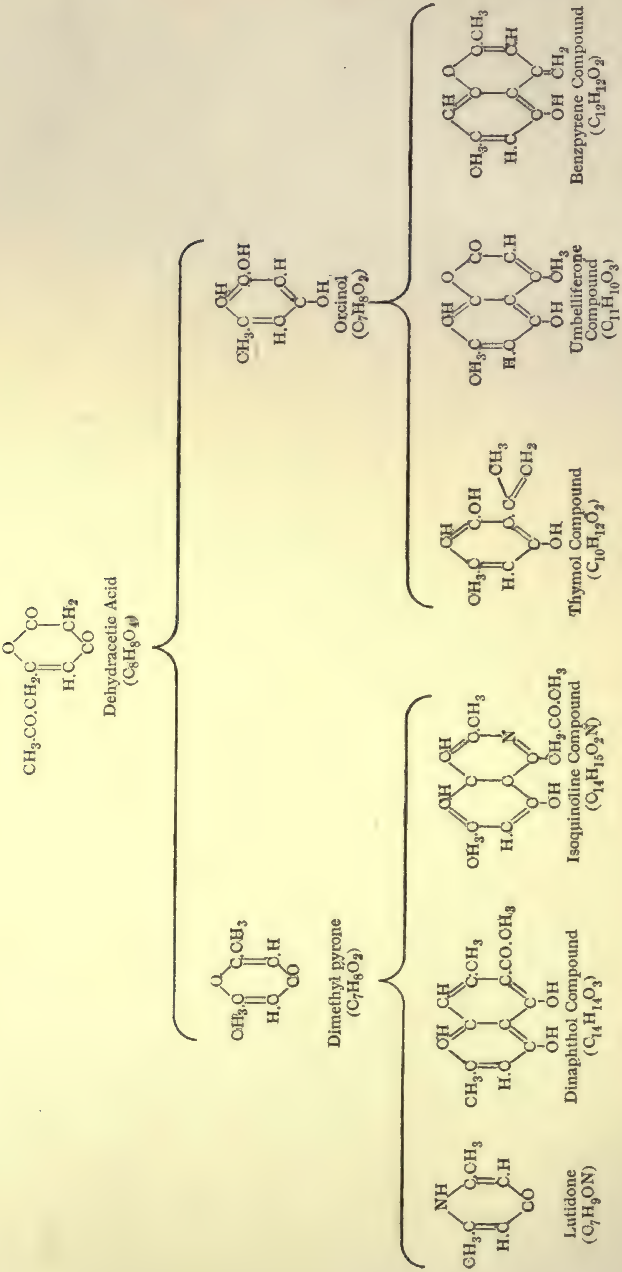
Collie[1] has obtained the diacetyl derivative of this substance by another method. When treated with acids it yields diacetyl-dimethyl-pyrone; whilst alkali converts it into di-acetyl-orcinol.

The foregoing reactions, of which a tabular scheme is given on page 248, are sufficient to show the manifold possibilities of the polyketide group. To complete the survey it is necessary to mention the ease with which the polyketides are hydrolyzed to simpler derivatives. Dehydracetic acid is decomposed by either acids or alkalis; and, if the hydrolysis be conducted under conditions which allow the intermediate products to be isolated, the following stages are observed:—



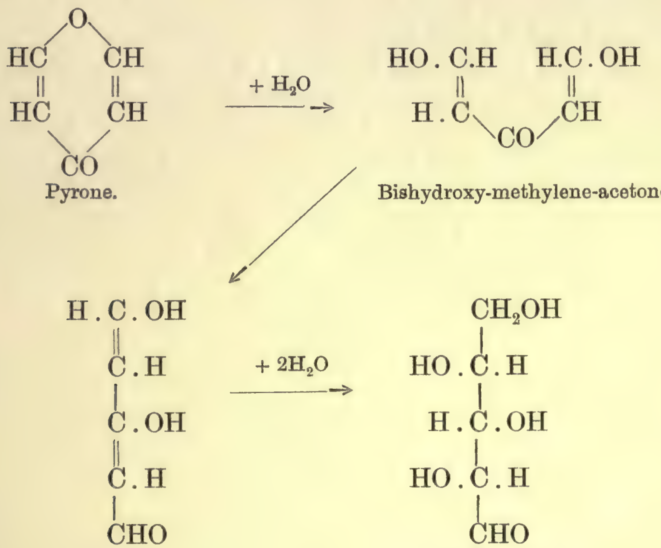
Dehydracetic acid. Triacetic lactone. Acetyl-acetone.

[1] Collie, *Trans.*, 1904, **85**, 971.


Dehydracetic Acid ($C_8H_8O_4$)
Dimethyl pyrone ($C_7H_8O_2$)
Orcinol ($C_7H_8O_2$)
Lutidone (C_7H_9ON)
Dinaphthol Compound ($C_{14}H_{14}O_3$)
Isoquinoline Compound ($C_{14}H_{15}O_2N$)
Thymol Compound ($C_{10}H_{12}O_2$)
Umbelliferone Compound ($C_{11}H_{10}O_3$)
Benzpyrene Compound ($C_{12}H_{12}O_2$)

8. *The Relations between the Carbohydrates and the Polyketides.*

Pyrone is acted upon by metallic alcoholates with the formation of derivatives of bishydroxy-methylene-acetone.[1] The proper conditions for carrying out a similar reaction with a water molecule instead of one of sodium ethylate have not yet been discovered; but the point is not without theoretical interest, as it suggests a means whereby sugars may be converted into polyketides and *vice versa*. Taking the case of pyrone as an example, the following stages would be involved :—



Pyrone. Bishydroxy-methylene-acetone.

A pentose.

A reverse series of reactions would lead from the carbohydrates to the polyketides and thence to all the classes of compounds which were enumerated in the last section.

Now, though it must be frankly confessed that up to the present our laboratory methods have failed to bring about either of these conversions,* there appear to be numerous data

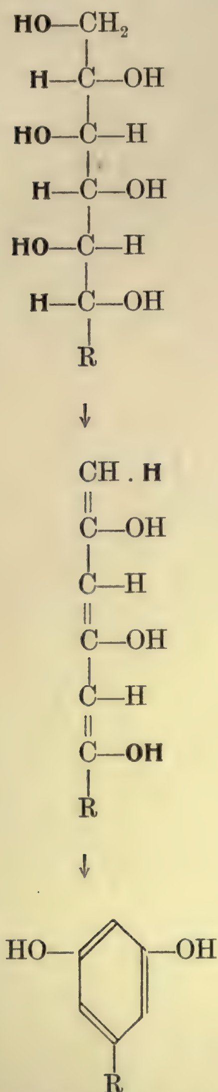
[1] Willstätter and Pummerer, *Ber.*, 1905, **38**, 1461.

* One great difficulty in the way is the ease with which open-chain derivatives of the polyketide series are hydrolyzed in presence of alkali or acid.

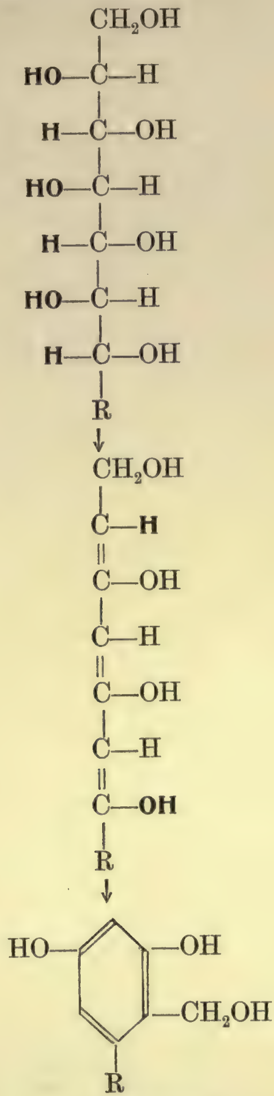
tending to show that many plant products are derived from polyketide chains; and since the carbohydrates form the most obvious source of polyketide derivatives it seems not unwarranted to assume that reactions similar to the above do take place in plants. If we do not make this assumption, we require so many different postulates in devising syntheses of vital products that the matter becomes extremely complicated; whereas by granting the possibility of polyketide production it may be rendered very simple.

9. *The Carbohydrates, Polyketides, and Benzene Derivatives.*

† The aromatic series is strongly represented among plant products; and it seems evident that the source of the vegetable benzene compounds must be sought in the carbohydrates and celluloses of the plant. The formulæ below indicate how benzene derivatives might be produced direct from the carbohydrates by means of simple dehydration followed by intramolecular rearrangement. Only two examples are given, as they are intended as illustrations and not as a complete list of possible changes. The groups involved in the dehydrations are printed in heavy type to make the matter clear.

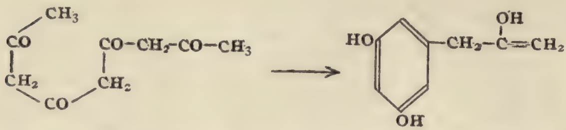


Orcinol derivative.



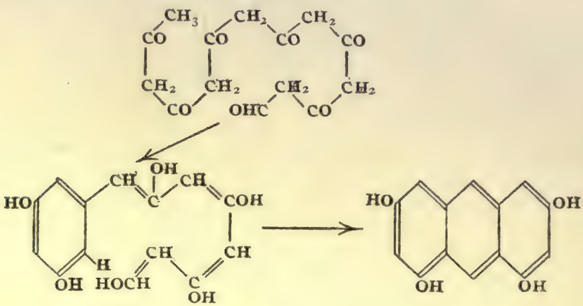
Ortho derivative.

† If the production of polyketides from the carbohydrates be assumed in order to simplify the formulæ, the following scheme shows how unsaturated side chains attached to benzene nuclei could be formed by dehydration and rearrangement :—



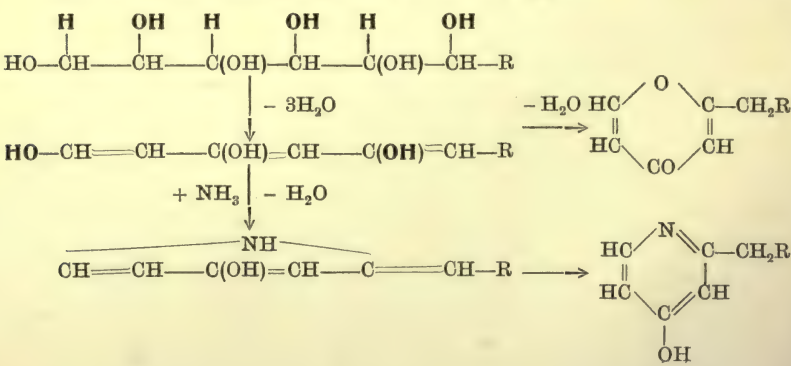
from which, by enzymatic reduction, an analogue of anethol would be formed.

† The production of anthracene derivatives could be accounted for in a similar manner:—



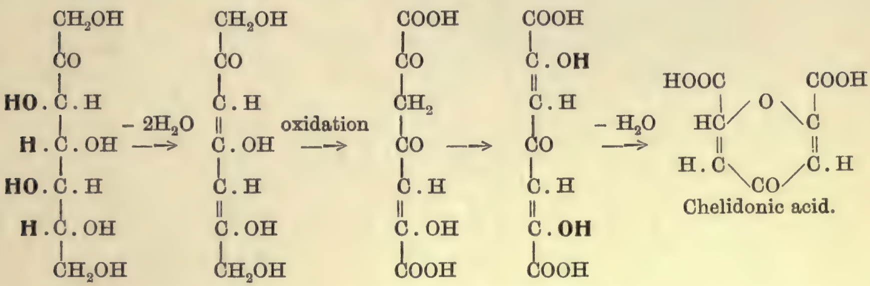
10. *The Formation of Pyrones and Pyridines from the Carbohydrates.*

The relations between the polyketides on the one hand and the pyrone and pyridine derivatives on the other have already been explained; so two examples will be sufficient to indicate the possibility of a direct passage from the carbohydrate series to the two heterocyclic groups. As before, the atoms involved in the dehydrations are printed in heavy type.



11. *The Genesis of some Plant Pigments.*

The fact that many of the important plant colouring materials belong to the pyrone group suggests that they may be derived from polyketide chains, and hence, indirectly, from the celluloses. In the simpler colouring matters the connection is almost obvious from an inspection of the formulæ; and one example will suffice. The case of chelidonic acid may be chosen, and its possible derivation from a heptose accounted for by the usual processes of dehydration and oxidation—

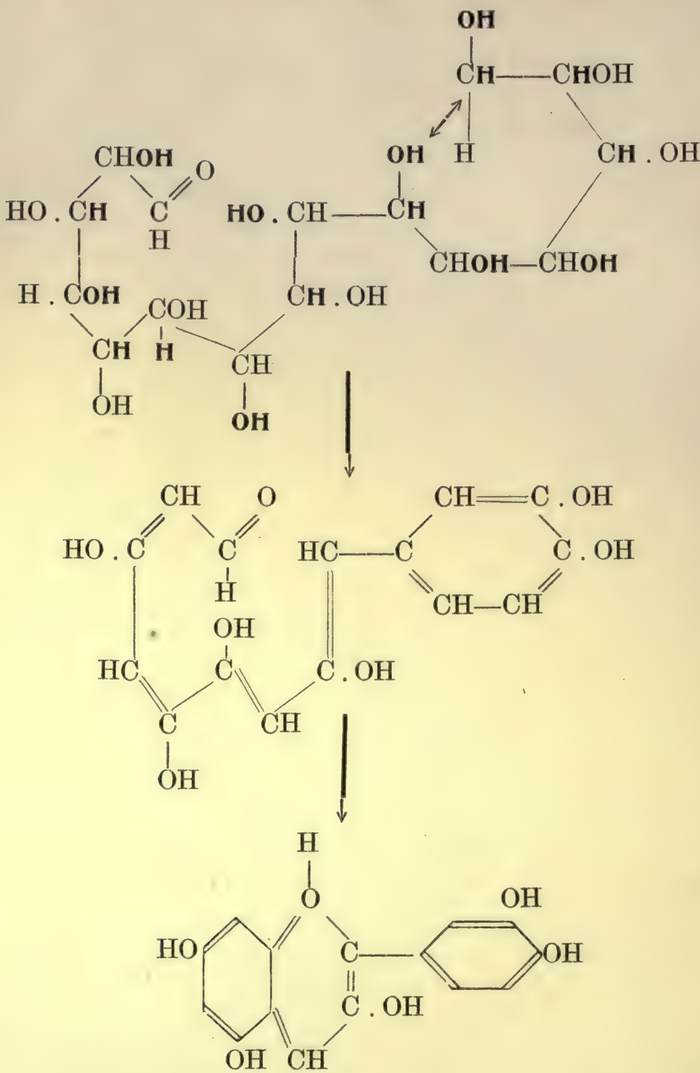


Chelidonic acid.

The benzo-pyrone group can be accounted for in a similar manner.

In the case of the anthocyanins, the reaction may be traced directly back to a carbohydrate chain without requiring the intermediate formation of a polyketide derivative at all. An examination of the formula of cyanidin, $C_{15}H_{12}O_6$, shows that it might be derived from a carbohydrate having the composition $C_{15}H_{30}O_{15}$ by the abstraction of nine molecules of water; and from cyanidin the corresponding anthocyanin is produced by the action of glucose. From the cyanidin, also, quercetin may be formed by oxidation; so that such a synthesis would open the way to the flavone series as well.

The following formulæ show how, by simple dehydration, it is possible to imagine the production of cyanidin from a carbohydrate of the structure $CH_2OH\,.\,(CH\,.\,OH)_{13}\,.\,CHO$. In order to make the steps clearer, the atoms eliminated by dehydration are printed in heavy type.



Cyanidin.

It is unnecessary to give further examples, as the reader can easily work them out for himself if he is interested in the point.

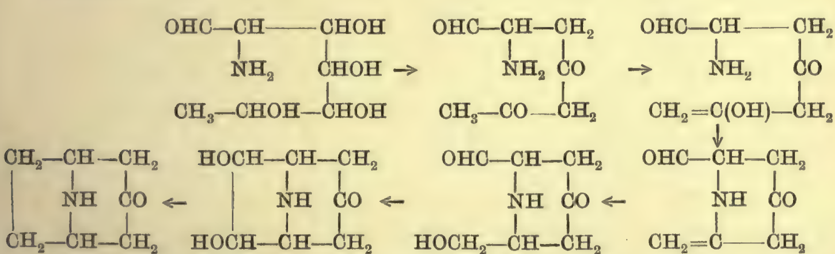
12. *The Alkaloidal Skeletons.*

With regard to the formation of the alkaloids, two views are possible. In the first place, the alkaloidal skeleton may be supposed to come into existence directly by the action of ammonia upon a long carbon chain derived from the celluloses; or, secondly, we may assume that the celluloses and proteins break down into smaller molecules which then take part in piece-meal syntheses of the larger alkaloid groupings. In either case, it will be seen that the production of alkaloids is to be regarded as a down-grade reaction.

The formation of tropinone furnishes a case to which both methods are applicable; so it may be given here as an example.

Let us assume that among the degradation products of cellulose a methyl-hexose-amine is produced. This will have the composition $C_7H_{15}O_5N$. Now nor-tropinone (i.e. tropinone without the methyl radicle attached to the nitrogen atom) has the composition $C_7H_{11}ON$. The difference between the two formulæ is H_4O_4; from which it is clear that dehydration alone will not suffice to pass from the one compound to the other; reduction to the extent of four hydrogen atoms is also necessary.

The steps in the conversion may be represented as follows:—



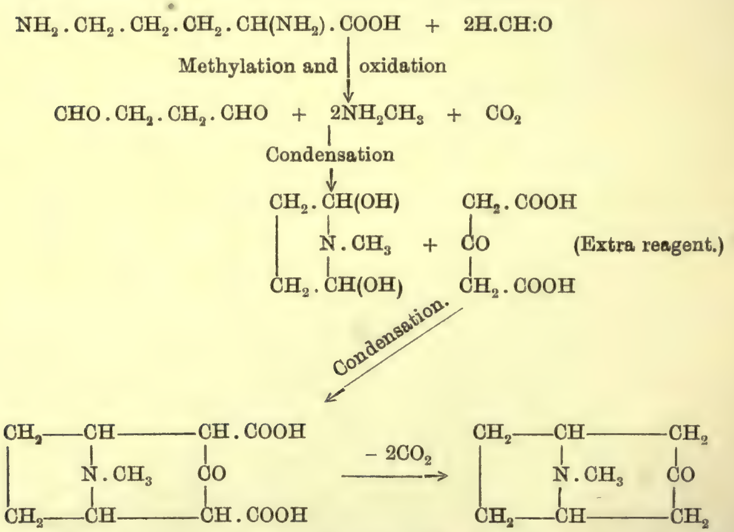
All the dehydrations and rehydrations involved in the process have not been indicated in the formulæ, as by this time the reader is probably sufficiently expert in appreciating the method to dispense with some of the steps. The last stage shown above consists in a reduction of the dihydric alcohol to a hydrocarbon grouping, which accounts for the four extra hydrogen atoms already mentioned. Having thus reached

nor-tropinone, methylation with formaldehyde would account for the production of tropinone itself.

Of course the order in the above series of changes might be varied, some of them coming earlier than is shown. The methylation of the nitrogen atom, for example, might take place much sooner than has been assumed.

Robinson[1] has put forward a series of suggestions as to the manner in which many of the familiar alkaloidal skeletons may be produced by using comparatively simple reactions; and his paper should be studied by all who are interested in the question. Unfortunately, it would lose by condensation, so cannot be dealt with here. In it examples are given of possible lines of syntheses in the pyrrolidine, piperidine, quinoline, and isoquinoline groups of alkaloids. Two reactions only are demanded as essential to the formation of the skeletons: the aldol condensation and the similar reaction between carbinolamines [containing the grouping $R_2 : C(OH) . N : R_2$] and compounds containing the radicle : CH . CO.

As an example of the method, we may choose the synthesis of tropinone—

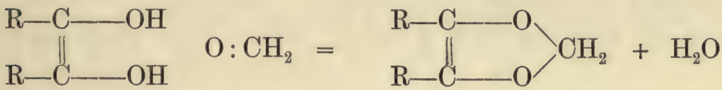


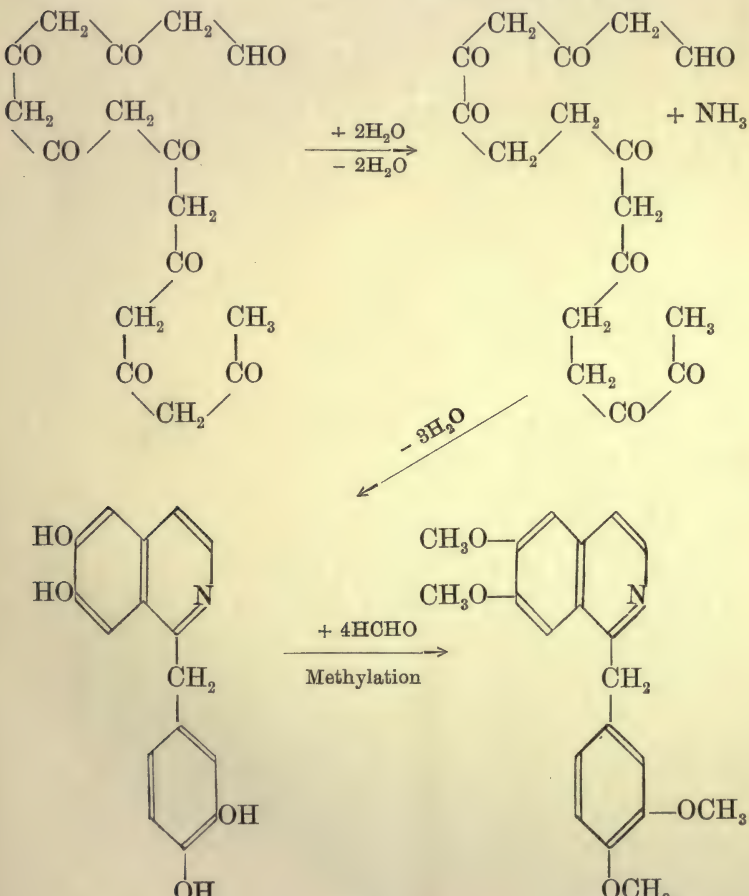
Robinson's synthesis of tropinone (see p. 132) has shown that reactions of the type required by his views can actually take place in practice under ordinary conditions.

[1] Robinson, *Trans.*, 1917, **111**, 876.

† Returning to the idea that the cellulose chain, *via* the polyketides, affords a source of alkaloid material, an example may be given of the course which the synthesis of papaverine might be expected to take. In the first place, it must be pointed out that by the usual process of dehydration and rehydration, it is possible to pass from the grouping $R.CO.CH_2.CO—$ to the arrangement $R.CH_2.CO.CO—$; and also that the formation of methoxyl radicles and methylene-ether groups may be supposed to take place by the action of formaldehyde :—

$$R—OH \quad + \quad 2CH_2O \quad = \quad R—O—CH_3 \quad + \quad H.COOH$$



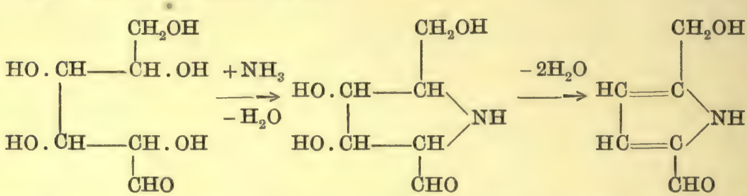


Papaverine.

13. *The Natural Syntheses of Pyrrol Derivatives.*

The importance of the pyrrol compounds from the standpoint of natural processes has already been indicated in an earlier chapter. The assimilative machinery of plants is bound up with chlorophyll; whilst hæmine plays an analogous part in the case of animals: and both these substances are built up on a basis of pyrrol rings. In addition to them, numerous other pyrrol derivatives are known to occur in the products of vegetable and animal metabolism: the pyrrolidine alkaloids and the bile acids are cases in point. It is therefore desirable to indicate here how these substances may be produced by vital reactions.

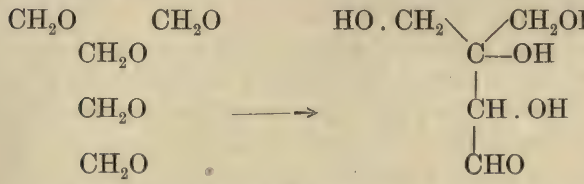
The carbohydrates probably form one source from which materials are drawn for pyrrol syntheses; whilst the nitrogen may be supplied either from ammonia or indirectly from the proteins. Assuming the presence of a sugar and ammonia, the synthesis of a pyrrol derivative may be accounted for by two dehydration reactions thus—



From a pentose, of course, a pyrrol with a single aldehydic side chain would be produced.

14. *Branched Chains and Terpene Compounds.*

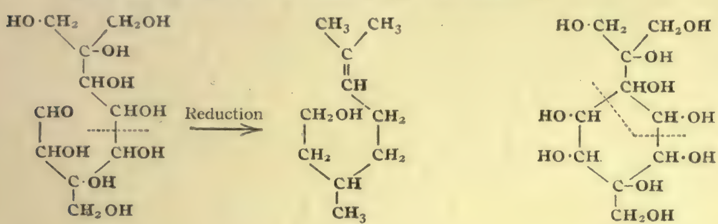
Hitherto we have confined our attention to carbohydrates in which the carbon atoms form a straight chain, but it seems desirable to indicate how forked chains may come into existence, as compounds of this type occur naturally along with straight-chain substances. The formation of apiose may be taken as an example. Its composition is $C_5H_{10}O_5$, and it might obviously be produced by the aldol condensation of five molecules of formaldehyde in the following manner;—



Apiose.

It seems difficult to imagine how apiose can be synthesized naturally in any other way.

But if this be granted, it becomes clear that terpene skeletons might be produced by an extension of the same series of condensations. Two possibilities are open. In the first place, two apiose nuclei may condense together giving the substance (I.) which by reduction may be transformed into an olefinic terpene derivative (II.); and from this, by intramolecular change similar to the geraniol-terpineol rearrangement (see p. 103), a terpene derivative might be formed. Or, alternatively, ten molecules of formaldehyde might condense together to produce a doubly-linked apiose chain (III.) from which terpenes might be formed by reduction.



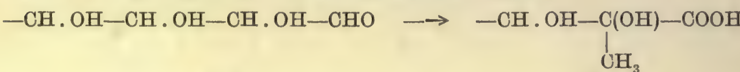
(I) (II) (III)

The particular terpene derivative formed would depend on the stage of oxidation of the original open-chain compound in the second case and also upon the position of the double bonds in the open chain.

Another possible line of synthesis of the terpenes is suggested by the production of a thymol derivative from the condensation products of orcinol and aceto-acetic ester (see pp. 246, 248). Since the orcinol and the aceto-acetic ester are both obtainable from polyketide chains, and hence possibly from carbohydrates; and since the thymol compound thus produced may be supposed to be reducible to a terpene, this line of thought leads also from the carbohydrates to the terpene group.

Finally it may be pointed out that a terpene $C_{10}H_{16}$ could be derived from a carbohydrate $C_{14}H_{28}O_{14}$ by the removal of four molecules of carbon dioxide and six molecules of water. In this case it would be necessary to assume as an intermediate compound one of those unsaturated acids which tend to lose their carboxyl radicles spontaneously.

Other reactions which might lead to the formation of a forked chain are the condensation of formaldehyde with a straight sugar chain and subsequent dehydration of the aldol thus produced; or the peculiar rearrangements in the sugar group observed by Kiliani,[1] whereby, under the action of lime-water, the group (I.) is transformed into (II.);

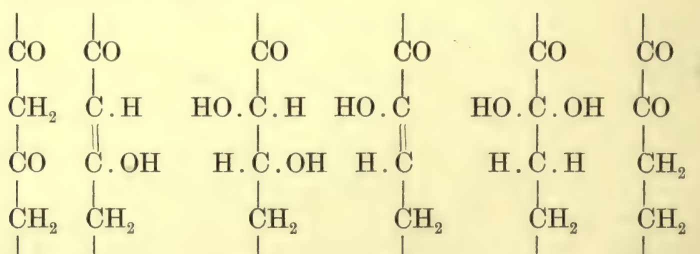


(I.) (II.)

or the analogous benzilic acid change.

15. *The Formation of the Fats.*

For the production of fats in the animal body the carbohydrates absorbed as food form the most probable source. We have already seen that sugars may be converted into polyketide chains by dehydration, so it is not necessary to give these steps. We may commence with the polyketide chain shown in (I.) as an example:—



(I.) (II.) (III.) (IV.) (V.) (VI.)

† If we take as our starting-point the group (I.) and convert it into the enolic form (II.), we can then add a molecule of water on to the double bond to form (III.). This substance could then be dehydrated to produce (IV.), to which water

[1] Kiliani, *Ber.*, 1884, **17**, 1302; 1905, **38**, 2668; 1908, **41**, 158, 469.

might be again attached, giving (V.), in which two hydroxyl groups are attached to the same carbon atom. This compound would lose a molecule of water, leaving (VI.).

† A comparison of the formulæ (I.) and (VI.) shows that the whole process implies a wandering of the hydrogen atoms to the lower end of the chain, and a corresponding migration of the oxygen atoms to the other. This purely theoretical series of actions could then be repeated, and the final result would be a loss of carbon dioxide from one end of the chain, and a building up of an aliphatic chain at the other end. Some such process may take place in the living organism during the formation of oils or fats,* and the liberation of carbon dioxide in respiration would be explicable in the same way.

Evidence in favour of this conception of the formation of fats from carbohydrates is obtained when the results of the reverse process are examined. In the disease pentosuria, the body fats are broken down and converted into sugars. Now, if this process involved the decomposition of the fat, with subsequent assimilation in the organism, then a synthesis of the pentose and, finally, its excretion, we should expect to find that the inactive fat had been converted into an *optically active* sugar owing to the intervention of the asymmetric components of the body tissues, etc. On the other hand, if the fat is converted direct into the sugar by the converse of the process sketched above—*i.e.* if the process involves a mere passage from Stage VI. to Stage I.—then, owing to the continual formation of enolic forms and consequent loss of asymmetry, the products of the fatty decomposition would not be active. In actual practice it is found that the arabinose excreted by patients suffering from pentosuria is the racemic form [1] of the compound; and this notwithstanding the fact that the organism is quite capable, even in that state, of decomposing *l*-arabinose if this sugar be given in food. It seems evident, therefore, that the arabinose excreted by such patients cannot have passed through the ordinary channels, but must have been produced directly from fat by some simple reaction such as is shown above. Further, the occurrence of aceto-acetic acid and acetone along with sugar in the urine

* Or wax in the case of bees.

[1] Neuberg, *Ber.*, 1900, **33**, 2243.

of patients suffering from diabetes proves that polyketide derivatives make their appearance during the disease.

16. *Syntheses and Degradations of the Proteins.*

In the foregoing sections we have dealt very fully with the carbohydrates and their possible mutations; so that it will be necessary to devote only a small space to the proteins, that second great class of up-grade products of the vital machinery. Fischer's researches on the polypeptides[1] leave little doubt that the protein molecules contain long chains of amino-acids coupled together in the form of amides; and it remains to suggest methods whereby such substances could be synthesized from simple materials within the living organism.

As in the case of the carbohydrates, our knowledge of the initial steps in the process is incomplete. Nitrates appear to be assimilated by the plant and reduced to nitrites; but uncertainty exists as to the further fate of the nitrite when it has been formed. The most suggestive experiments on the subject appear to be those of Baudisch.[2] On exposing potassium nitrate to diffused daylight, he found that it was reduced to potassium nitrite. Under the same conditions, potassium nitrite, when mixed with formaldehyde or methyl alcohol, became converted into hyponitrite and then, by the action of more methyl alcohol, was changed into the potassium salt of formohydroxamic acid:—

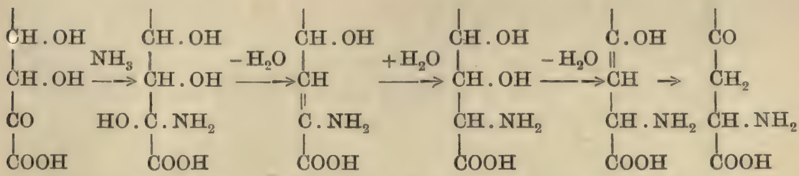
$$CH_3OH + KNO_2 = HO.CH:N.OK + H_2O.$$

Prolonged exposure to light resulted in a further reduction, ammonia being formed.

According to Baudisch, ammonia in plants is oxidized by oxidases or by ultra-violet light, and the resulting product combines with formaldehyde to form aci-nitromethane which, being a reactive substance, takes part in vegetable syntheses.

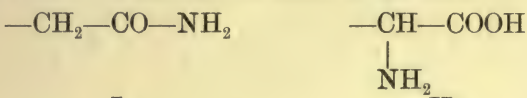
If we assume the presence of ammonia and carbohydrates, however, the further reactions may be formulated in other ways. Suppose that among the sugars formed are some which contain the group —CO.COOH, which may be produced by oxidases from aldoses. The synthesis of amino-acids may then be supposed to take the course shown below:—

[1] See p. 180.
[2] Baudisch, *Ber.*, 1911, **44**, 1009.



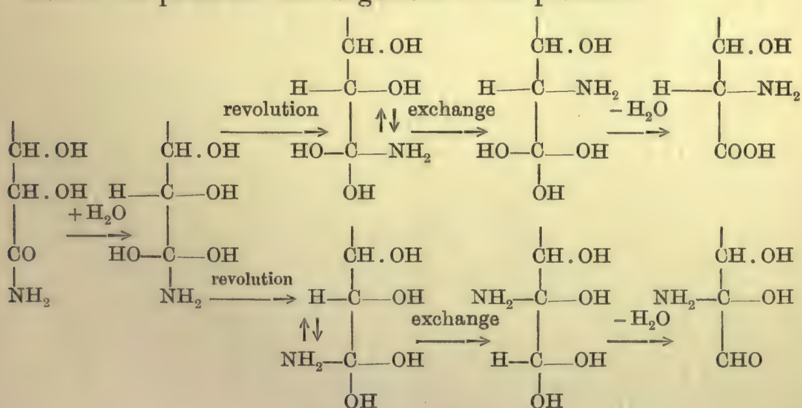
In support of this view, it may be pointed out that a carbonyl group in the *a*-position to a carboxyl radicle is exceptionally reactive;[1] which would give a clue to the reason for the natural amino-acids having their amino-group in the *a*-position. It will be noticed that only the first steps in the formation of the hydrocarbon chain are given above; but a repetition of hydration and dehydration would lengthen it to any required extent.

Instead of assuming the direct formation of an amino group, we may postulate that the first step in the synthesis of the proteins is the production of an amide. We are faced with a certain difficulty; for it is clear that an inversion of some kind must take place in order to convert the group (I.) into the group (II.), which entails the transference of the nitrogen atom from one carbon atom to the next.



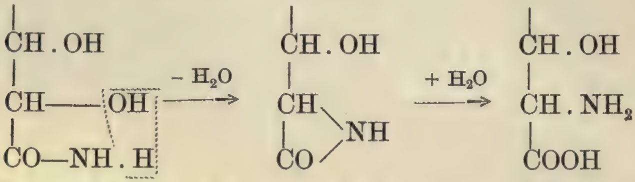
(I.) (II.)

† Such transferences are quite possible on lines with which we are already familiar. The following symbols show the application of the pinacone rearrangement to the problem—



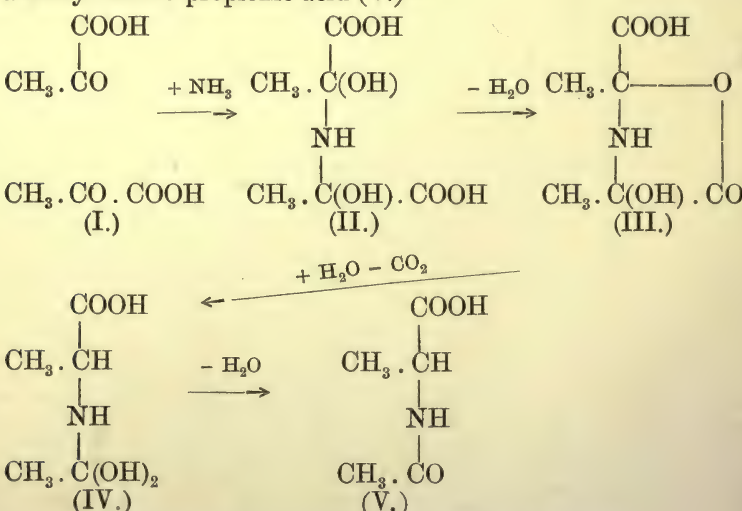
[1] Stewart, *Trans.*, 1905, **87**, 185.

Another method by which the transference of the nitrogen atom to the neighbouring carbon might be accomplished is by the temporary production of a three-membered ring which, as soon as formed, might open up again in a new place. In this way the reaction is reduced to the simple subtraction and readdition of a molecule of water—



The production of the original amide radicle may be attributed to the formation and partial hydrolysis of a cyanhydrin of the sugar; for hydrocyanic acid is known to be formed in plants in quantities sufficient to yield the required cyanhydrins.

Much more probable than either of the above suggestions is the following, which is based upon an observation of de Jong[1] in the case of pyruvic acid. When ammonium pyruvate is mixed with pyruvic acid the reaction takes the following course. In the first place the two pyruvic molecules (I.) react with ammonia from the ammonium salt to form an imino compound (II.). This substance then loses water, and forms the lactone (III.). A molecule of water is then taken up and carbon dioxide is split off, yielding the substance (IV.), which immediately eliminates another molecule of water, producing *a*-acetyl-amino-propionic acid (V.)—



[1] De Jong, *Rec. trav. chim.*, 1900, **19**, 259; 1904, **23**, 131.

Now it will be seen that this reaction leads to the formation of the type of amino-acid most common among the protein derivatives—the α-amino-acid; for the acetyl group could easily be hydrolyzed away by enzyme action.

The application of this to more complex cases is not difficult. It will be remembered that in the section dealing with the formation of fats it was pointed out that a very simple process would lead from the carbohydrates of the type $R—CH.OH—CH.OH—CH.OH—CH.OH—CHO$ to derivatives of the structure $R—CH_2—CH_2—CO—CO—COOH$. Oxidation of the latter would yield homologues of pyruvic acid, the number of carbon atoms in the group R depending upon the length of the carbohydrate chain which serves as a raw material. Once these pyruvic acid derivatives have been produced, there is no reason why they should not undergo de Jong's reaction and form the corresponding α-amino-acids; and in this way the raw materials for polypeptide and protein syntheses might be produced.[1]

In connection with the protein syntheses, another point of interest arises, though it must be classed as a purely speculative one. If two molecules of formaldehyde could be induced to condense together in the following manner, keten would be formed; and from this, by polymerization, chains of polyketides might be formed:—

$$H_2C:O + H_2C:O = H_2O + CH_2:C:O$$

Now, similarly, we might devise a synthesis in the nitrogen group—

$$NH_3 + (HO)_2C:O = 2H_2O + NH:C:O$$

This compound is, of course, isomeric with cyanic acid.

† For present purposes, however, our interest in it arises from the fact that it is obviously the nitrogen analogue of keten—

$$CH_2:C:O \qquad\qquad NH:C:O$$

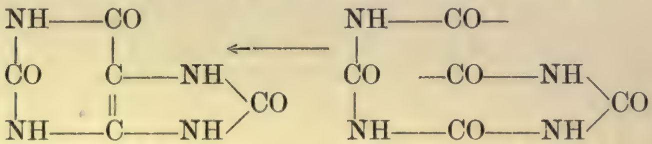
and, from this similarity, we may term the compound aziketen. Now just as keten can polymerize to long chains which then add on water to form polyketides, so aziketen should

[1] For other suggestions see Haas and Hill, *Chemistry of Plant Products*, p. 333 ff.

polymerize and hydrate in order to produce the simplest type of polypeptide—

$$NH_2—CO—NH—CO—NH—CO—NH—COOH$$

† It is at this point desirable to bring the matter into touch with actual practice. If we examine the formula of uric acid, it requires no great stretch of imagination to recognize that the purine compounds are derivatives of this type of polypeptide, probably produced from the open-chain compound by reduction accompanied by ring formation—



Thus the break-down of the sugars into the various aromatic and pyrone derivatives would find its analogue in the formation of the uric acid derivatives from the proteins.

† Another suggestion as to the production of purine derivatives by vital processes may be put forward. In the break-down of proteins, amino-acids of the type $R—CH(NH_2)—COOH$ are formed. Now in the oxidation of these, it is possible that the hydrocarbon chain R is burned away first, leaving behind the potential —NH . CO— portions, which may then unite to form uric acid and its derivatives.

17. *Conclusion.*

In this chapter an attempt has been made to sketch certain methods by which natural products may possibly come into existence in the organism, but it cannot be too strongly emphasized that they are intended merely as suggestions and not as dogmatic attempts to settle the problems involved. If they have brought to the notice of the reader the questions which arise in this branch of chemistry and have inspired any desire to go further into the matter, they have amply fulfilled the object for which they were written. We are at present far from a definite knowledge of how the vital machine carries out its work; but if the ideas collected in the present chapter induce the reader to speculate for himself on the subject, he will find a most fascinating field open to him.

One point which certainly comes into prominence in the foregoing pages is the fact that, by a series of hypothetical dehydrations and rehydrations, it is easy to see how very different types of grouping might be produced. A system which is capable of accounting for the production of such widely varying materials as benzene derivatives, pyrrols, pyridine derivatives, pyrones, anthocyanins, fats and alkaloids has evidently something more than mere plausibility behind it. We are not yet able to carry out these changes in the laboratory, except in the case of the polyketide derivatives; but it will be surprising if sooner or later some experimental evidence is not found to bear out much that has been advanced in the preceding sections.

† Should the reader wish to pursue speculations in this field the following questions may serve to guide his attention to some hitherto unsolved problems. The fatty acids of the acetic series are quite common in nature, whilst their hydroxy-derivatives — with the exception of lactic acid — are hardly represented at all. Why should this be so? Why do all the important sugars and starches contain a chain of five or six *or a multiple of five or six* carbon atoms? Why are the majority of the amino-acids obtained from the proteins the α-amino-acids? Why are the ortho- and meta-derivatives so strongly represented among naturally occurring benzene derivatives, whilst the majority of the terpenes are derived from *para*-cymene?

† In the case of such broad generalities there must surely be some simple solution. The curious thing is—not that the answers to these questions are omitted from the ordinary text-books, but rather that the questions themselves do not appear to have suggested themselves to the writers at all.

CHAPTER XI.

SOME AROMATIC DERIVATIVES OF ARSENIC.

1. *Introductory.*

In order to understand the immense expansion of our knowledge of the aromatic arsenic compounds during the last decade, it is necessary to turn to the field of chemo-therapy, which was opened up by Ehrlich's work on sleeping sickness. This disease is caused by the presence of a micro-organism called a trypanosome, which infests the blood of patients; and in order to effect a cure, it is necessary to destroy the parasites. It was found that the methods of serum-therapy, which, in other diseases, had proved invaluable, failed in this case; and Ehrlich therefore cast about for some drug which would prove fatal to the trypanosome. His first investigations led him to the project of injecting patients with certain dyes which had the power of staining the micro-organisms; for clearly a direct action of the reagent upon the trypanosome could thus be assured. Good results were obtained from trypan-red and trypan-blue; but a further examination proved that these dyes, though effective in the body, had no toxic effect upon trypanosomes in a test-tube. It therefore became clear that the dyes in themselves were not deadly to the microbes; but that in the body they became altered in some way which conferred a toxic power upon them. Now arsenic compounds have a most deleterious influence upon trypanosomes, and Ehrlich endeavoured to combine the fixing effect of the dye with the toxic effect of arsenic by injecting patients simultaneously with trypan-red and sodium arsenate in the hope of producing a joint action of the two reagents. From this he was led on to abandon the use of the dye altogether and press into service various organic compounds of arsenic which appeared to combine in themselves both

fixing power and toxic influence. The result of his earlier discoveries in this field drew him to synthesize a very great number of aromatic arsenic derivatives; and his work[1] has stimulated investigation of this field to a marked degree.

2. *The Nomenclature of Arsenic Derivatives.*

Since this chapter deals only with the organic acidic derivatives of arsenic and some related compounds, it is unnecessary to give a complete scheme of nomenclature for all the known series; it will be sufficient to indicate the names of the classes which will require mention in the following pages.

If, in arsenic acid, we imagine the hydroxyls replaced in succession by phenyl radicles, we shall obtain the following series:—

$$O:As\begin{cases}OH\\OH\\OH\end{cases}\qquad O:As\begin{cases}C_6H_5\\OH\\OH\end{cases}\qquad O:As\begin{cases}C_6H_5\\C_6H_5\\OH\end{cases}\qquad O:As\begin{cases}C_6H_5\\C_6H_5\\C_6H_5\end{cases}$$

Arsenic acid. Phenylarsenic acid. Diphenylarsenic acid. Triphenylarsenic oxide.

From arsenious acid, by a similar substitution, we obtain phenyl-arsenious oxide:—

$$O:As—OH \qquad O:As—C_6H_5$$

Parallel to azobenzene, we have arsenobenzene:—

$$C_6H_5—N:N—C_6H_5 \qquad C_6H_5—As:As—C_6H_5$$

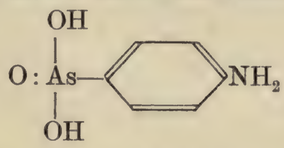
3. *The Syntheses of the Arylarsinic Acids and Oxides.*

The influence of erroneous observations in retarding the advance of our knowledge has seldom been better exemplified than in the case of the organic arsenic compounds. In 1863 Béchamp[2] heated together aniline and arsenic acid and produced a compound which he described as an anilide of arsenic acid. In point of fact, however, he actually had in his hands the first representative of an entirely new class of compounds which would have attracted attention had their true nature been known; but his description of the substance as an anilide failed to stimulate any interest, and the matter rested there

[1] For accounts of Ehrlich's researches see his general paper (*Ber.*, 1909, **42**, 1), and also his obituary notice (*Ber.*, 1916, **49**, 1223).

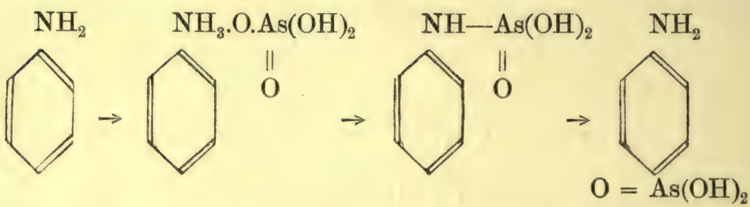
[2] Béchamp, *Compt. rend.*, 1863, **56**, 1173.

for over forty years. In 1907 Ehrlich,[1] in his search for arsenic derivatives of therapeutic value, repeated Béchamp's experiment and found that the compound was not an anilide but was instead an acid, *p*-aminophenylarsinic acid :—



Further investigation showed that the reaction was a general one, so that members of the new series were readily prepared. It was discovered that phenols also can be used instead of amines, so that two new classes lay open to research.

It is found that when either an aromatic amine or a phenol is treated with arsenic acid, so long as the para-position is free of substituents, the arsenic atom attaches itself there. The mechanism of the reaction probably includes the primary formation of an addition product at the amido-group, followed by the elimination of water and a wandering of the arsenic residue to the para-position, if that be vacant—



When the amido-compound is already para-substituted (*e.g.*, in the case of *p*-toluidine) the arsenic residue is forced to take up a position ortho to the amido group;[2] but in this case the yields are much smaller than is the case with unsubstituted analogues. The only important exception to this rule is *p*-nitraniline, which gives a good yield of 5-nitro-2-aminophenylarsinic acid when heated with arsenic acid.[3]

If an excess of amido-compound be used, the reaction does not stop short with the formation of the primary product; but, instead, a further interaction occurs between the already-formed arsinic acid and the extra amine of the reaction-

[1] Ehrlich and Bertheim, *Ber.*, 1907, **40**, 3292.
[2] Benda, *Ber.*, 1909, **42**, 3619. [3] *Ibid.*, 1911, **44**, 3293.

mixture. Another hydroxyl group of the arsinic acid is displaced by the amidophenyl nucleus, with the production of a diarylarsinic acid—[1]

$$\underset{\text{Aniline.}}{NH_2 . C_6H_4 . H} + \underset{p\text{-Amidoarsinic acid.}}{HO{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{As}}{-}C_6H_4 . NH_2} \xrightarrow{-H_2O} \underset{\text{Di-}p\text{-amidoarsinic acid.}}{NH_2 . C_6H_4{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{As}}{-}C_6H_4 . NH_2}$$

From the foregoing brief description of this reaction between arsenic acid and amino-compounds it must not be assumed too readily that the matter is quite without difficulties. As is well known, arsenic acid in certain circumstances acts as a good oxidizing agent with amino-benzene derivatives (for example in the synthesis of fuchsine), so that the conditions must be carefully chosen in the case of the arsinic acid syntheses in order that there may not be too great a loss of material.

From the aminophenylarsinic acids it is possible to prepare other classes of compound by taking advantage of the usual reactions of the amino-group. Thus by the use of methyl sulphate the amido hydrogens may be replaced by methyl radicles;[2] acetic anhydride yields an acetyl derivative of the arsinic acid;[3] the half-anilide of oxalic acid is produced by the action of the acid on the amino-group;[4] a carbamide derivative can be prepared by acting on the aminoarsinic acid with cyanic acid or its esters;[5] whilst by means of the diazo-reaction the arsinic acid nucleus may be coupled with various amines or phenols.

So much for the substituted phenylarsinic acids. We must now turn to the preparation of the parent substances. These cannot be obtained so simply as their derivatives; since arsenic acid does not attack the unsubstituted hydrocarbons of the benzene series so easily as it acts upon the hydroxy or amido derivatives. Instead, it is necessary first to prepare arylarsine tetrahalides and then decompose these by means of water.

The preparation of phenylarsinic acid will suffice as an

[1] Benda, *Ber.*, 1908, **41**, 2367. [2] D.R.P. 204664.
[3] Ehrlich and Bertheim, *Ber.*, 1907, **40**, 3296.
[4] Bertheim, *Ber.*, 1911, **44**, 3092. [5] D.R.P. 213155.

illustration of the various steps. Mercury diphenyl is acted upon by arsenic chloride to produce phenyldichloroarsine—

$$(C_6H_5)_2Hg + 2AsCl_3 = 2C_6H_5AsCl_2 + HgCl_2$$

By the action of chlorine this dichloro compound is converted into a tetrachloro derivative:—

$$C_6H_5 . AsCl_2 + Cl_2 = C_6H_5 . AsCl_4$$

When this last substance is acted on by water, it yields the required acid—

$$C_6H_5 . AsCl_4 + 3H_2O = C_6H_5 . AsO(OH)_2 + 4HCl$$

In order to avoid the necessity of actually forming the tetrachloride it is possible to combine two reactions into one by treating the dichloroarsine with chlorine in presence of water, when the following reaction occurs:—

$$C_6H_5 . AsCl_2 + Cl_2 . + 3H_2O = C_6H_5 . AsO(OH)_2 + 4HCl$$

Secondary arsinic acids, containing two aromatic nuclei attached to the arsenic atom, are obtained by analogous reactions in which the starting-points are raw materials of the structure R_2AsCl.

If we imagine that all three hydroxyl groups in arsenic acid are replaced by aryl radicles, we arrive at the structure of the triaryl arsine oxides, $R_3As : O$. These substances are prepared by the action of alkali upon the halides or oxyhalides of the tertiary arsines. In this way tertiary arsinehydroxides are formed, which, on heating, break down into the required oxides. Thus in the case of triphenylarsine oxide[1] the changes are as shown below:—

$$(C_6H_5)_3AsCl_2 \xrightarrow{\text{Alkali}} (C_6H_5)_3As(OH)_2 \xrightarrow{-H_2O} (C_6H_5)_3As : O$$

4. *The Reactions of the Group* —$AsO(OH)_2$ *in the Arsinic Acids.*

An inspection of the formulæ of the arsinic acids shows that they contain a quinquevalent atom of arsenic. By the use of reducing agents, the arsenic can be converted into the trivalent form, giving rise to arsine oxides (I.), arsenoaryl derivatives (II.) and even, in some cases, arsines (III.)—

$$\text{(I.) } R . As : O \qquad \text{(II.) } R . As : As . R \qquad \text{(III.) } R_3As$$

[1] La Coste and Michaelis, *Annalen*, 1880, **201**, 243; Michaelis, *ibid.* **321**, 164.

The reagents used depend upon the structure of the raw material and of the particular stage to which it is desired to carry the reduction. Among the most useful are sodium amalgam in methyl alcohol, sodium hyposulphite, stannous chloride in concentrated hydrochloric acid, and sulphur dioxide. In the case of the last two a little hydriodic acid may be employed as a catalyst.

One example will suffice to illustrate the various stages in the reduction. When *p*-amidophenylarsinic acid * is reduced by sulphur dioxide in presence of hydriodic acid the reaction takes the form shown in the equation below, the hydriodic acid playing the part of carrier for the sulphur dioxide, which reduces the iodine formed in the reaction to hydriodic acid again—

$$\underset{p\text{-Aminophenylarsinic acid.}}{NH_2 . C_6H_4 . AsO(OH)_2} + 2HI \rightleftharpoons \underset{p\text{-Aminophenylarsenious oxide.}}{NH_2 . C_6H_4 . As : O} + 2H_2O + I_2$$

The oxide may be precipitated from the solution by adding ammonia.

The conversion of the oxide into triamino-triphenyl arsine [1] is accomplished by heating with dilute hydrochloric acid—

$$3NH_2 . C_6H_4 . As : O \longrightarrow (NH_2 . C_6H_4)_3As + As_2O_3$$

When concentrated hydrochloric acid is substituted for the dilute variety, the reaction takes a different course, resulting in the formation of the hydrochloride of *p*-amidophenylarsine dichloride, $NH_2 . C_6H_4 . AsCl_2,HCl$.

Thus by means of these reactions it is possible to change the group $R . AsO(OH)_2$ into $R . AsCl_2$ and R_3As.

An intermediate stage in the reduction can be attained by submitting *p*-amidophenylarsenious oxide (I.) to the action of sodium amalgam in methyl alcohol. In this way,[3] 4 : 4′-diamidodihydroxyarsenobenzene (II.) is formed first; whilst the reaction reaches its end with the production of 4 : 4′-diamidoarsenobenzene (III.) :—

$$\underset{\text{(I.)}}{NH_2 . C_6H_4 . As : O} \rightarrow \underset{\text{(II.)}}{NH_2 . C_6H_4 . As(OH) . As(OH) . C_6H_4 . NH_2}$$
$$\rightarrow \underset{\text{(III.)}}{NH_2 . C_6H_4 . As : As . C_6H_4 . NH_2}$$

One of the most curious reactions of the arylarsinic acids

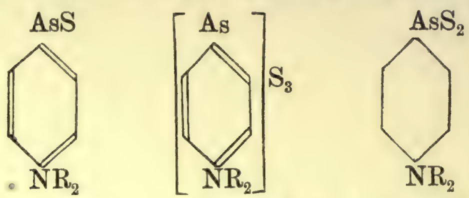
* The sodium salt is actually employed instead of the acid.

[1] Ehrlich and Bertheim, *Ber.*, 1910, 43, 923. [3] D.R.P. 206057.

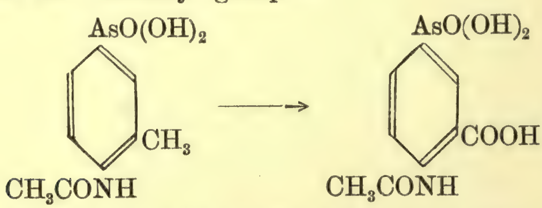
is that which they undergo when treated with halogens. Normally the group $—AsO(OH)_2$ appears to be firmly attached to the aryl nucleus; but when an aqueous solution of *p*-amidophenylarsinic acid is treated with bromine water, the bond between the carbon and arsenic atoms is broken so readily that a practically quantitative yield of symmetrical tribromo-aniline is produced. It is only with the greatest care that halogen derivatives of the arsinic acids can be obtained by direct halogenation.

Nitration, on the other hand, can be readily carried out; and the nitro derivatives thus obtained can be reduced to amido compounds by the usual methods.

The action of sulphuretted hydrogen[1] upon the arylarsinic acids produces sulphides of the following characters:—



Finally, a reaction of the methyl homologues of arylarsinic acids may be mentioned. When they are oxidized by alkaline potassium permanganate, the methyl radicles are converted into carboxyl groups—



so that in this way it is possible to prepare carboxylic acids of this series.[2]

5. *The Arsenobenzene Compounds.*

Among the compounds which have recently sprung into prominence owing to their pharmacological importance, the arsenobenzene derivatives take a high place; and in addition

[1] D.R.P. 205617.

[2] Adler, *Ber.*, 1908, **41**, 931; Kahn and Benda, *ibid.*, 3859.

to this their relation with the azo compounds lends theoretical interest to their character.

Two methods for synthesizing them were already mentioned in the last section: the reduction of arylarsenious oxides or of arylarsinic acids. In addition to these a third process may be mentioned, which consists of allowing primary arsines to act upon either arsenious oxides or upon chloro-arsines:—

$$R . AsH_2 + R . As : O = R . As : As . R + H_2O$$
$$R . AsH_2 + R . AsCl_2 = R . As : As . R + 2HCl$$

The arsenobenzene derivatives are pale yellow in colour. With iodine they form di-iodo addition products—

$$R . As : As . R + I_2 = R . AsI . AsI . R$$

Chlorine converts them direct into chloro-arsines—

$$R . As : As . R + 2Cl_2 = 2R . AsCl_2$$

Sulphur acts upon arsenobenzene to form phenylarsine sulphide—

$$C_6H_5 . As : As . C_6H_5 + 2S = 2C_6H_5 . As : S$$

whilst the further action of sulphur produces anomalously diphenylsulphide—

$$C_6H_5 . As : As . C_6H_5 + 4S = As_2S_3 + (C_6H_5)_2S$$

An even more complete break-down is produced by heating arsenobenzene with ammonium sulphide or hydriodic acid; benzene is formed—

$$3C_6H_5 . As : As . C_6H_5 + 3H_2S = 6C_6H_6 + As_2S_3 + As_4$$
$$3C_6H_5 . As : As . C_6H_5 + 6HI = 6C_6H_6 + 2AsI_3 + As_4$$

The differences in behaviour between the arseno-compounds and the azo-derivatives is very strongly marked. As can be seen from their formulæ there is a close similarity in structure between the two classes—

$$R . As : As . R \qquad\qquad R . N : N . R$$

The first difference which strikes the observer is that exhibited by the colours of the substances. Azobenzene is deep red in tint, whilst arsenobenzene is pale yellow. Evidently the group —As : As— is a much weaker chromophore than the radicle —N : —. Again, azobenzene is one of the most stable substances with which we are acquainted; whilst arsenobenzene is so reactive that it must be preserved in sealed

tubes to avoid oxidation by the air. Azobenzene can be distilled without alteration; but arsenobenzene when heated above its melting-point breaks down into arsenic and triphenylarsine—

$$3C_6H_5 . As : As . C_6H_5 = 2(C_6H_5)_3As + As_4$$

The azo-compounds are crystalline substances, whereas some of the arsenobenzene derivatives show colloidal properties.

The foregoing facts are sufficient to show how great a change is produced by substituting the group —As : As— for —N : N—; and it seems curious that such a marked alteration in properties should be brought about by the substitution for one element of another so closely allied to it according to our ideas of chemical classification. Possibly the semi-metallic character of the arsenic atom is involved; but at present we have no means of explaining the deviation in properties which has been observed.

6. *Some Arsenic Compounds of Therapeutic Value.*

The study of drugs derived from arsenic has, in recent years, been extended over such a wide field that it is impossible to deal with the question as a whole in this place.[1] All that will be attempted is to survey a few of the more important data which have been obtained.

The simplest arsenic derivative with which we need deal is the sodium salt of 4-aminophenylarsinic acid, $NH_2 . C_6H_4 . AsO(OH)(ONa)$. This compound is known technically as Atoxyl or Soamin. It is prepared by the general method of heating aniline with arsenic acid and then adding alkali to the acid thus formed until a neutral reaction is shown with litmus.

The therapeutic action of atoxyl presents some points of interest. When it is allowed to act upon the trypanosomes which produce sleeping sickness, it is found that if the action be carried out in a test-tube, even a 1-2 per cent. solution of atoxyl has no effect upon the organisms. On the other hand, in the human body a concentration of 1 in 120,000 is sufficient to destroy the trypanosomes. How are we to explain this apparent anomaly? Ehrlich's solution is as follows. Quinque-

[1] See Bertheim, *Handbuch der organischen Arsenverbindungen.*

valent arsenic has no effect upon trypanosomes, as there is no valency free by which the arsenic can anchor itself to the trypanosome structure. Hence in the test-tube no action is observed. In the animal organism, however, the atoxyl is acted upon and converted partly into *p*-aminophenylarsenious oxide, $NH_2 . C_6H_4 . As : O$, which contains trivalent arsenic and therefore has a certain amount of latent valency on the arsenic atom. This substance attacks the trypanosomes; and to its existence must be ascribed the therapeutic value of atoxyl.

Further investigation of the properties of atoxyl as a cure for trypanosomiasis or syphilis have not realized the hopes originally founded upon it. In order to make it effective large doses have to be used; and in such quantities atoxyl exhibits certain deleterious actions which reduce its healing value considerably. Thus blindness may be produced in the patient; and it is found that even when matters do not go so far as this yet there are always minor sequelæ of the treatment which are the more dangerous owing to the fact that, like radium burns, they take a long time to make themselves outwardly felt. Further, atoxyl solutions are not sufficiently stable to permit of their being sterilized by boiling previous to an injection being made. On grounds such as these, atoxyl has ceased to command the attention which it once attracted; and it has been replaced by other compounds of more general interest.

The search for a substitute led to the utilization of acetylatoxyl, technically known as Arsacetin. This substance is simply atoxyl in which one of the amino-group's hydrogen atoms is replaced by the acetyl radicle—

$$CH_3 . CO . NH . C_6H_4 . AsO(OH)(ONa)$$

Its toxicity is much lower than that of the parent substance, for it is three to ten times less poisonous for certain species of animals; whilst on the other hand its therapeutic value is practically the same as that of atoxyl itself. Further, it is stable in boiling water, so that its solutions can be sterilized. Unfortunately, it possesses, though in a minor degree, the evil influence of atoxyl on the optic nerve and on other parts of the organism, so that its value is limited also.

Another anilide, *p*-benzenesulphonyl-aminophenylarsinic

acid, $C_6H_5 . SO_2 . NH . C_6H_4 . AsO(OH)_2$, was put on the market under the name of Hectin; but it was found that it produced deafness. A compound of it with mercury, known as Hectargyre, met with no better fate.

A further proof that toxicity is not necessarily a measure of physiological effects is found in the case of 3, 4-diaminophenylarsinic acid. The introduction of the second amino-group into the benzene nucleus reduces the toxicity of the substance twenty-five times; but the objectionable subsidiary effects still persist and render the compound useless for pharmacological purposes.

We must now turn to the arseno-compounds. Arsenophenyl-glycine is the first with which we need concern ourselves. It is prepared in the following way. Sodium *p*-aminophenylarsenate is boiled in aqueous solution with chloracetic acid, being kept saturated with hydrochloric acid gas during the process. In this way phenylglycine-arsinic acid is formed—

$$(HO)_2OAs . C_6H_4 . NH_2 + Cl . CH_2 . COOH = (HO)_2OAs . C_6H_4 . NH . CH_2COOH + HCl$$

When this new acid is reduced in aqueous solution with excess of sodium hydrosulphite in presence of magnesium salts, it yields arsenophenyl-glycine—

$$HOOC . CH_2 . NH . C_6H_4 . As : As . C_6H_4 . NH . CH_2 . COOH$$

This substance is found to be of much greater efficiency against trypanosomes than any of those which have already been mentioned; and further, its toxicity is much lower than that of the other drugs. Not only so, but it has the power of attacking trypanosomes which appear to have acquired immunity against atoxyl or arsenacetin.

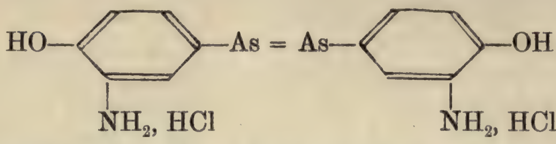
To explain these facts, Ehrlich put forward the following ideas. In order to kill a trypanosome, it is necessary to anchor the drug to the organism chemically. This is done, according to Ehrlich's views, by means of some special grouping in the trypanosome structure which he termed a "receptor". These "receptor" groups are specific; that is to say they have an affinity for certain drugs but not for others. Now trypanosomes have at least two types of receptor in their structure: the arseno-receptor which can be attacked by trivalent arsenic and the acetico-receptor which

can anchor the acetic acid group. Thus a compound like arsenophenyl-glycine has a double grip on the trypanosome: one jaw of the forceps (to use a crude analogy) being formed by the trivalent arsenic atom, whilst the second jaw is the group $—CH_2COOH$. Now in the case of the immunized trypanosomes Ehrlich assumes that the arsenic compound (atoxyl) is attacked both by the trypanosome and by the cell-material of the animal in whose blood the organisms are living; and if the trypanosome is slightly less avid of arsenic than the body-cells are, it will escape from the action of the drug, which will expend itself on the patient instead. But if the group $—CH_2 . COOH$ be present in the drug it acts principally on the parasite and not on the host, owing to the specific nature of the trypanosome acetico-receptor; and, once the drug is fixed on the parasite, the arsenic in it will come into play and destroy the trypanosome.

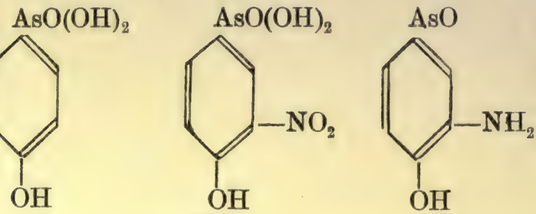
In actual practice arsenophenyl-glycine has a wonderful effect in the case of animals. An animal whose blood swarms with trypanosomes can be completely cured by a single injection. Unfortunately, the results are not so good in the case of the human patient in such ailments as sleeping sickness or syphilis.

Another substance which at first seemed to promise good results is *p*-arsenophenol: $HO . C_6H_4 . As : As . C_6H_4 . OH$, which is prepared from the sodium salt of *p*-hydroxyarsinic acid by reduction in aqueous solution with sodium hydrosulphite in presence of magnesium salts. It has a very powerful spirillocidic action; and, by introducing certain substituents into the benzene nuclei, this power can be enhanced still further. At the same time, however, the arsenophenol derivatives have great drawbacks. They are difficult to prepare pure; they have a high degree of toxicity; and their readiness to oxidize, yielding the highly poisonous phenol-arsenious oxide derivatives, forms an almost insuperable bar to their practical employment.

We now come to the most useful of all the arsenic derivatives, salvarsan or 606. This substance has the following structure:—



It is synthesized in the following manner. Nitric acid in theoretical quantity converts *p*-hydroxyphenylarsinic acid (I.) into the nitro-derivative (II.). Partial reduction of this yields 3-amino-4-hydroxyphenylarsenious oxide (III.). The action of sodium hydrosulphite upon this last substance produces the base of salvarsan, 3, 3′-diamino-4, 4′-dihydroxyarseno-benzene—



(I.) (II.) (III.)

The hydrochloride, salvarsan itself, is formed by dissolving the crude base in methyl alcohol and adding the calculated amount of hydrochloric acid dissolved in methyl alcohol. Care must be taken to exclude air throughout the process.

In the case of salvarsan, the deleterious actions on the organism which were noted in the case of other drugs are reduced to a minimum, though they still make themselves felt in some degree. The drug is of the greatest value as a weapon against the parasites which cause diseases such as sleeping sickness, syphilis, or malaria; and it is also employed in certain animal disorders. It requires great care in its administration, however, for slight impurities in the water used to dissolve it before injection may increase its toxicity to a serious extent. Numerous salvarsan derivatives have been prepared, such as neo-salvarsan.

7. *Conclusion.*

From the facts described in the foregoing sections it will be seen that, in addition to therapeutic problems, the aromatic arsenic compounds are not without theoretical interest. The

stability of the carbon-arsenic linkage in the presence of certain reagents and its weakness when attacked by others, would form an interesting subject for speculation. The difference in behaviour may be due to internal salt formation in the case of the substituted acids; but we have no data upon which to base conclusions at the present time.

Again, the extraordinary difference in properties between arsenobenzene on the one hand and azobenzene on the other suggests that a comprehensive examination of the three allied compounds—

$C_6H_5 . P : P . C_6H_5$	$C_6H_5 . N : N . C_6H_5$	$C_6H_5 . As : As . C_6H_5$
Phosphobenzene.	Azobenzene.	Arsenobenzene.

might lead to results of considerable importance.

CHAPTER XII.

TRIVALENT CARBON.

1. *Triphenylmethyl.*

ANYONE who glances through the journals of the chemical world for the last few years must be struck by the enormous production of new compounds which is at present going on; and, if he reflects at all, he will be driven to ask himself what criterion should be applied in order to distinguish the really important substances from what we may term the by-products of synthetic chemistry. Clearly the only fate which can overtake the majority of these new compounds is that their dossiers will be "neatly tucked away in Beilstein, the Abstracts published by the various Chemical Societies, or in other equally convenient depositories of information". They will remain at best in a dormant condition, waiting the time when some *Analogie-arbeit* necessitates a knowledge of their properties. On the other hand, those new bodies which have any interest apart from their melting-points soon become centres of new research; and the more important of them usually lead to investigations extending far beyond the constitution and properties of the original compound. For example, the researches which more than a generation ago took their rise in the constitution of aceto-acetic ester have not yet reached their final stages.

This ramification of interest has seldom been so strongly marked within recent years as in the case of the substance termed triphenylmethyl; and it is the rapid extension of the field of research in this division of the subject which makes any treatment of the triphenylmethyl problem difficult. In the present chapter, it will be necessary to confine ourselves as far as possible to the narrow question of the constitution of triphenyl-

methyl and only to touch lightly upon the wider questions which are closely bound up with it.

The discovery of triphenylmethyl resulted from an attempt to prepare hexaphenyl-ethane, which was made by Gomberg [1] in 1900. He allowed "molecular" silver to act upon triphenyl-bromo-methane, and obtained a compound which he naturally supposed to be hexaphenyl-ethane; for the reaction would normally have taken the course expressed in the formulæ below—

$$2\,(C_6H_5)_3C\,.\,Br + 2\,Ag = (C_6H_5)_3C - C(C_6H_5)_3 + 2\,AgBr$$

On analysis, however, the substance is found to have about 6 per cent. too little carbon to agree with the hexaphenyl-ethane formula; and further examination showed that it could not be a hydrocarbon at all, but must contain oxygen.

This oxygen might have been introduced in either of two ways: it might have been imported through the silver used in the reaction; or it might have been derived from the air. The experiments were therefore repeated, other metals, such as zinc and mercury, being used instead of silver; and still the resulting substance was found to be oxygenated. From this it was clear that atmospheric oxygen was the source of the oxygen in the end-product; and further experiments were made in which precautions were taken to exclude air from the apparatus. The end-product in this case differed from that which had previously been obtained; and on analysis it was found to have the composition corresponding to hexaphenyl-ethane.

An examination of its properties, however, brought Gomberg to the conclusion that the substance which he had obtained could not be hexaphenyl-ethane; for he had expected that that body would be an extremely stable compound, whereas his synthetic hydrocarbon was very reactive.

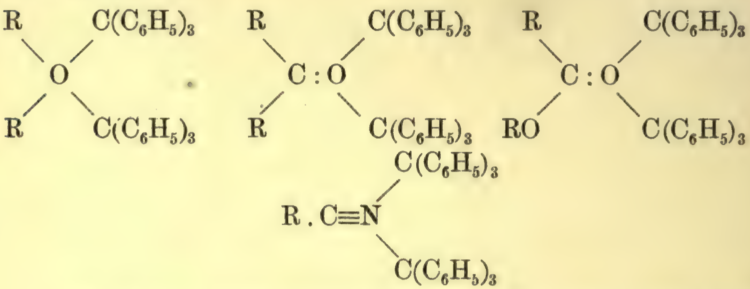
At this point we may give a *résumé* of the chief properties of the hydrocarbon. When first prepared, it is a colourless crystalline solid, which dissolves with great readiness in most organic solvents, giving yellow solutions. Even at zero it reacts with iodine to form triphenylmethyl iodide. Exposure to the air even for a short time is sufficient to transform it

[1] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

into a peroxide; and Gomberg[1] has been able to prove that this same peroxide can be produced by the action of sodium peroxide on triphenyl-chloro-methane (but not by the spontaneous oxidation of triphenylmethyl chloride or of triphenyl carbinol under the same conditions). From this we may deduce that the peroxide has the constitution—

$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

The hydrocarbon forms double compounds[2] with ethers, esters, ketones, nitriles, or aromatic hydrocarbons (and amylene), the composition of these substances corresponding to one molecule of ether (or of the other substances) plus one molecule of hexaphenyl-ethane. Gomberg ascribed the formation of the oxygenated derivatives to the change of the oxygen from the divalent to the quadrivalent condition, and formulated the constitution of the substances generally as derivatives of the following types:—



The fact that these substances are actually compounds and not simply mixtures in which the ether or other body is held mechanically is proved by the fact that similar compounds are formed with carbon disulphide and chloroform, and these latter bodies can be heated to 110° C. in a stream of carbon dioxide without giving up their full content of chloroform or disulphide. With sodium, the hydrocarbon forms a brick-red compound[3] having the formula $(C_6H_5)_3C . Na$ which is very reactive.

There is one further point to which we must draw attention, though it does not directly concern the hydrocarbon. It has

[1] Gomberg, *Ber.*, 1900, **33**, 3150. [2] *Ibid.*, 1905, **38**, 1333, 2447.
[3] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.

been shown[1] that the halogen salts, such as triphenylmethyl chloride $(C_6H_5)_3C.Cl$, and triphenylmethyl bromide $(C_6H_5)_3C.Br$, when dissolved in solvents such as liquid sulphur dioxide which have strong dissociating power, have conductivities very nearly equal to that of methylamine hydrochloride. This proves that in the yellow solutions obtained in this way, the compounds are split up into two ions, one of which must be $(C_6H_5)_3C$.

From the data which we have given in the preceding paragraphs, it is clear that the problem of the constitution of Gomberg's synthetic hydrocarbon opens up a wide field for speculation; and numerous attempts have been made in recent years to discover the solution. Four views have at one time or another gained a certain amount of support, and we shall deal with these in turn in the following sections.

2. *The Trivalent Carbon Hypothesis.*

The reactions of his synthetic hydrocarbon—which we may for the sake of convenience term triphenylmethyl—led Gomberg[2] to put forward the view that the substance contained one carbon atom attached to three phenyl radicles, but having no fourth radicle attached to it:—

$$\begin{array}{l} C_6H_5\diagdown \\ C_6H_5{-}C \\ C_6H_5\diagup \end{array}$$

The fourth valency of the carbon atom may be supposed to be free, or to be absorbed by the residual valency of the three phenyl groups. This conception of a trivalent carbon atom is really not so extraordinary as it seems; for we might consider that ethylene derivatives contain two adjacent carbon atoms of this type, instead of writing their structural formulæ as we usually do with a double bond between the two unsaturated carbons.

In favour of this constitutional formula for triphenylmethyl we may urge the evidence derived from the reactions of

[1] Walden, *Ber.*, 1902, **35**, 2018; Gomberg, *ibid.*, 2045. Compare Gomberg, *Ber.*, 1905, **38**, 1342.

[2] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

the substance with iodine and with oxygen, both of which can be expressed quite simply :—

$$\begin{array}{l} (C_6H_5)_3C \\ (C_6H_5)_3C \end{array} + \begin{array}{c} I \\ | \\ I \end{array} = \begin{array}{l} (C_6H_5)_3C\,.\,I \\ (C_6H_5)_3C\,.\,I \end{array}$$

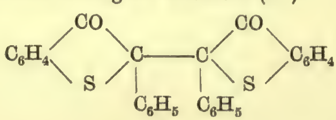
$$\begin{array}{l} (C_6H_5)_3C \\ (C_6H_5)_3C \end{array} + \begin{array}{c} O \\ \| \\ O \end{array} = \begin{array}{r} (C_6H_5)_3C—O \\ | \\ (C_6H_5)_3C—O \end{array}$$

And we might also adduce the simplicity of the formulæ for the double compounds of triphenylmethyl with ethers, ketones, nitriles, etc.

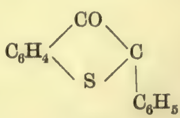
All that this amounts to, however, is that we can express these reactions in a straightforward manner on the assumption of trivalent carbon.* If we can express them equally convincingly by means of a formula containing only quadrivalent atoms, then we should be entitled to reject the trivalent carbon view as adding an unnecessary assumption to our usual ones.

But there are facts which conflict with the trivalent carbon view. Gomberg and Cone[1] have shown that the three phenyl radicles do not possess identical properties, as they should do if the substance actually had the triphenylmethyl structure. We need only outline their proof here, as we shall have to return to it in a later section. By subjecting para-rosaniline to Sandmeyer's reaction they obtained tri-*p*-bromo-triphenyl carbinol, which, by the action of hydrochloric acid, was transformed into tri-*p*-bromo-triphenylmethyl chloride—

* Kalb and Bayer (*Ber.*, 1913, **46**, 3879) state that 2, 2′-diphenylthioindigo white (I.) dissociates in solution into two free radicles each containing trivalent carbon and having the structure (II.)—

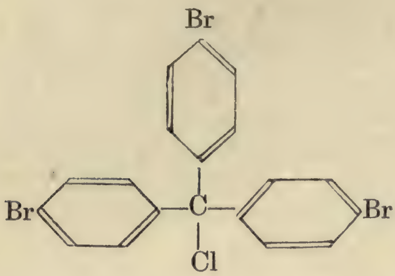


(I.)

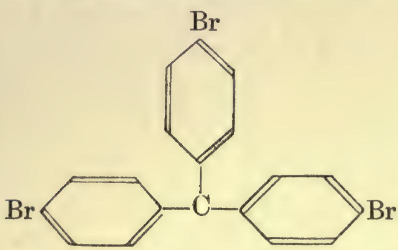


(II.)

[1] Gomberg and Cone, *Ber.*, 1906, **39**, 3274.



When this substance was treated in the usual way with silver, it gave a substance analogous to triphenylmethyl. This new compound formed a peroxide just as triphenylmethyl does, and therefore (if the trivalent carbon idea be correct) we may safely assume that it is tri-*p*-bromo-triphenylmethyl—



Now the tri-*p*-bromo-triphenyl chloride was sealed up in an air-free flask with excess of molecular silver, and the whole was shaken for a considerable time. At the end of this, it was found that the silver had removed all the chlorine (reaction of triphenylmethyl formation), but in addition it had abstracted one atom of bromine from the ring of one of the phenyl groups. Since there was excess of silver present, if all the three phenyl radicles had identical properties we should expect that they would yield up their bromine simultaneously. Further, the new compound produced by the elimination of bromine was not a peroxide similar to that formed by triphenylmethyl, nor did it yield such a peroxide when exposed to air. The experiments were repeated with other halogen derivatives of triphenylmethyl, and led in these cases to similar results. It is thus shown: (1) That the substitution of three bromine atoms in the position para to the "trivalent" carbon of triphenylmethyl in no way interferes with the activity of the substance; (2) further action of silver eliminates only one of the three

bromine atoms, so that one nucleus differs from the other two. From (1) the complete analogy between triphenylmethyl and its tribromo-derivative is clear; and hence we are entitled to draw the conclusion that the inference in (2) is valid also for the parent hydrocarbon. But if in triphenylmethyl we have one phenyl nucleus endowed with properties not shared by the other two, it is evident that a symmetrical formula—

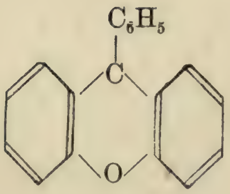
$$\begin{array}{l} C_6H_5\diagdown \\ C_6H_5{-}C \\ C_6H_5\diagup \end{array}$$

cannot give a true representation of the substance's properties.

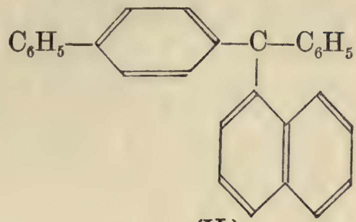
A further complication is introduced into the problem by a consideration of the molecular weight of triphenylmethyl in solution. If we assume that the free radicle triphenylmethyl, $C_{19}H_{15}$, is present, then the molecular weight should be 243; whereas if hexaphenyl-ethane is formed, its molecular weight ought to be 486. Actual experiments show that in naphthalene at 80° C. the molecular weight is 414; whilst in benzene near 0° C. it appears to be 480-485.[1] These results suggest that under certain conditions the hexaphenyl-ethane dissociates to some extent into triphenylmethyl radicles.

This idea has received further support from the work of Schlenk[2] on other compounds of the triphenylmethyl type. Thus the molecular weight of phenylxanthyl (I.) is 257 for the monomolecular (trivalent carbon) form and 514 for the bimolecular (quadrivalent carbon) substance. The actual value found in benzene by the ebullioscopic method is 279; pointing to the probability that 82 per cent. of the substance exists in the solution as a free radicle whilst only 18 per cent. of the bimolecular form is present. Again, phenyl-biphenyl-a-naphthylmethyl (II.) should have a molecular weight of 369 for the free radicle and 738 for the bimolecular form. In boiling benzene the actual value determined was 362, which proves that the substance exists under these conditions as the free radicle.

[1] Gomberg and Cone, *Ber.*, 1904, **37**, 2037; 1906, **39**, 3274.
[2] Schlenk, *Annalen*, 1912, **394**, 178.



(I.)



(II.)

It has been shown by Piccard[1] that the colour of triphenylmethyl solutions in ether deepens on dilution,* which suggests that the lowering of the concentration is accompanied by an increase in the dissociation of the bimolecular form; whilst Gomberg and Schoeffle[2] have studied the influence of the constitution of the triarylmethyls upon their degree of dissociation.

The foregoing evidence is thus somewhat confusing. On the one hand, it proves that triphenylmethyl cannot be symmetrical in structure; and on the other side it establishes the fact that the triarylmethyl derivatives do actually exist in solution in the form of free radicles. It is clear that we must seek further if we are to find a satisfactory solution of the problem.

3. *The Hexaphenyl-ethane Hypothesis.*

When Gomberg's hydrocarbon was first prepared, its properties were found to be so different from what had been expected of hexaphenyl-ethane that the latter structure was at once dismissed as incapable of giving a proper representation of the reactions of the new substance; but as time went on, and more information with regard to the properties of the more highly phenylated ethanes was acquired, it seemed as if the earlier view had been rather hasty, and that there was a certain

[1] Piccard, *Annalen*, 1911, **381**, 347; compare Hantzsch, *ibid.*, **384**, 135; 1913, **398**, 379.

[2] Gomberg and Schoeffle, *J. Amer. Chem. Soc.*, 1917, **39**, 1652.

* Normally, of course, dilution has no influence on absorptive power since the light-ray passes through the same number of molecules in either concentrated or dilute solutions, provided that the thickness of the layer is kept directly proportional to the degree of dilution. This is known as Beer's Law.

amount of probability in the idea that Gomberg's compound was, after all, merely hexaphenyl-ethane.

For two years, however, this view was kept in abeyance, owing to the fact that Ullmann and Borsum [1] had synthesized a substance which they regarded as hexaphenyl-ethane. This body was obtained by reducing triphenyl carbinol; and its properties corresponded to some extent with those which had been anticipated for hexaphenyl-ethane. In 1904, however, Tschitschibabin [2] established the constitution of this supposed hexaphenyl-ethane, proving it to be a compound of the following structure:—

$$(C_6H_5)_3C—C_6H_4—CH(C_6H_5)_2$$

The removal of the supposed hexaphenyl-ethane from the literature thus left open the possibility that Gomberg's triphenylmethyl really had the hexaphenyl-ethane structure; and Tschitschibabin [2] put this suggestion forward, basing his views on the following considerations.

In the first place, we have to account for the reactivity of triphenylmethyl, and show why a compound of the hexaphenyl-ethane structure should be reactive. Tschitschibabin pointed out that an accumulation of electro-negative atoms or radicles in a molecule tends to make it much less stable. For example, Zincke showed that the accumulation of chlorine atoms in the phenol molecule leads to its degradation into simpler substances. Again, spatial factors sometimes come into play and cause a saturated substance like trimethylene to behave as if it were an unsaturated hydrocarbon. These considerations show that we must be prepared for certain anomalies and must beware of judging problems of constitution on too rigid lines. Further, it is not necessary to assume an unsaturated structure for triphenyl-methyl merely in order to account for its ready reaction with oxygen to form a peroxide, for Gomberg [3] himself has shown that the fully saturated analogue triphenyl-iodomethane reacts in a similar manner. Nor is this all; for when we examine more carefully the behaviour of the highly phenylated ethane derivatives we shall find that they are

[1] Ullmann and Borsum, *Ber.*, 1902, **35**, 2877; Gomberg, *ibid.*, 3914.
[2] Tschitschibabin, *Ber.*, 1904, **37**, 4709.
[3] Gomberg, *Ber.*, 1902, **35**, 1836.

by no means so stable as analogy would lead us to expect. Tschitschibabin[1] has proved that even below its melting-point pentaphenyl-ethane is attacked by air; at a temperature of only 150° C. hydrochloric acid in benzene solution acts on it so powerfully that the bond between the two ethane carbon atoms is broken, and such products as tetraphenyl-ethane, triphenyl-methane, and triphenyl-chloro-methane, are formed; whilst Cone and Robinson[2] found that the action of phosphorus pentachloride in boiling benzene broke down the pentaphenyl derivative into triphenylmethyl chloride.

Against the hexaphenyl-ethane hypothesis we may adduce several arguments. In the first place, triphenylmethyl is a colourless solid, but its solutions are deep yellow in tint: no ordinary benzenoid derivative is known which behaves in this way. Stronger evidence is to be found in the work of Gomberg (mentioned in the previous section), by which he showed that one phenyl group had properties different from those of the others. The ordinary hexaphenyl-ethane formula gives no indication of this. Thirdly, Gomberg[3] has proved that his hydrocarbon can easily be converted into that which was obtained by Ullmann and Borsum. On the hexaphenyl-ethane hypothesis, this reaction would take the following course, which is parallel to that which is taken in the semidine change—

$$(C_6H_5)_3C\,.\,C\begin{cases}C_6H_5\\ C_6H_5\\ C_6H_4\,.\,H\end{cases} \longrightarrow (C_6H_5)_3C\,.\,C_6H_4\,.\,CH\begin{cases}C_6H_5\\ C_6H_5\end{cases}$$

$$R\,.\,C_6H_4\,.\,NH\,.\,NH\,.\,C_6H_4\,.\,H \longrightarrow R\,.\,C_6H_4\,.\,NH\,.\,C_6H_4\,.\,NH_2$$

But Jacobson,[4] the greatest authority on the benzidine and semidine changes, regards such a change in the triphenylmethyl series as most unlikely. Lastly, we have already seen that one of the most marked characteristics of triphenylmethyl is its capacity for forming double compounds with solvents;

[1] Tschitschibabin, *Ber.*, 1907, **40**, 367.
[2] Cone and Robinson, *Ber.*, 1907, **40**, 2160.
[3] Gomberg, *Ber.*, 1902, **35**, 3918; 1903, **36**, 376.
[4] Jacobson, *Ber.*, 1904, **37**, 196.

but no such property seems to be possessed by compounds analogous to hexaphenyl-ethane.

From the foregoing paragraphs, it is clear that most of the arguments both in favour of and against the hexaphenyl-ethane view depend to some extent upon analogy; and we must be careful not to lay too much stress upon them unless we are satisfied that the analogies really hold good. If we rule out the arguments based upon what a compound "ought" to do, it will be seen that the evidence remaining—Gomberg's differentiation between the phenyl nuclei—tells against the hexaphenyl-ethane hypothesis.

4. *Quinonoid Hypotheses.*

If we reject the two hypotheses which we have dealt with in the preceding sections, it is clear that we have still a third possibility open to us: for both the triphenylmethyl view and the hexaphenyl-ethane explanation were based on the assumption that the phenyl nuclei in triphenylmethyl were benzenoid in character; so that by assuming a quinonoid structure for the substance we shall arrive at totally different types of formulæ. The quinonoid conception of triphenylmethyl was put forward very early in the compound's history by Kehrmann—[1]

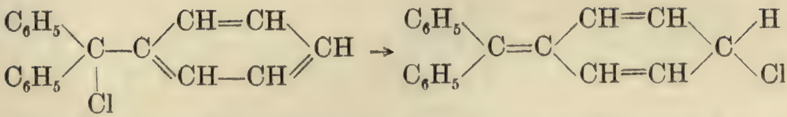
$$C\begin{array}{l}\diagup CH=CH \diagdown \\ \diagdown CH=CH \diagup\end{array}C=C(C_6H_5)_2$$

This suggestion, involving as it does the assumption of a divalent carbon atom, meets with little approval at the present time; and since other formulæ of the quinonoid type have since been suggested which do not necessitate such a postulate, we need not deal further with this one.

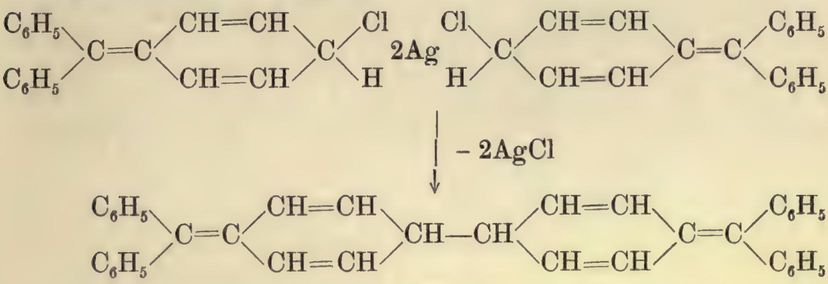
In 1903 Heintschel[2] put forward a new suggestion. On his hypothesis, the first step in the synthesis of triphenylmethyl is the conversion of triphenyl-chloro-methane into a desmotropic form in which the chlorine atom has been shifted into a position para to the methane carbon atom—

[1] Kehrmann, *Ber.*, 1901, **34**, 3818; see also Norris and Sanders, *Am. Chem. J.*, 1901, **25**, 117; and Gomberg, *Ber.*, 1902, **35**, 1824.

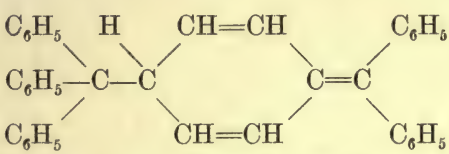
[2] Heintschel, *Ber.*, 1903, **36**, 320, 579.



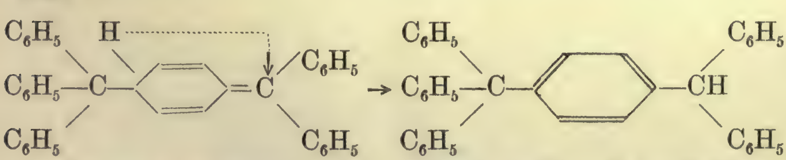
By the action of metals, two chlorine atoms are withdrawn from two molecules of the chloro-compound, and in this way triphenylmethyl is produced—



An examination of Heintschel's formula will show that it contains two quinonoid phenyl nuclei. Jacobson[1] proposed to modify this, making only one phenyl group quinonoid, as shown below—



This view makes triphenylmethyl a derivative of a substance approaching the quinole type; and as the reactivity of the quinoles is quite abnormal, we might expect considerable reactive power from a body having the structure proposed by Jacobson. The change of the Gomberg hydrocarbon into the substance prepared by Ullmann and Borsum can also be easily explained on this hypothesis, as the wandering of a single hydrogen atom is sufficient to account for the isomerization—

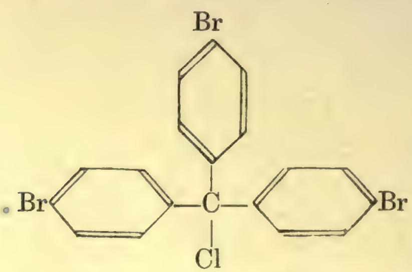


Gomberg's hydrocarbon. Ullmann and Borsum's hydrocarbon.

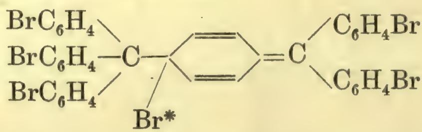
[1] Jacobson, *Ber.*, 1904, **37**, 196.

The Jacobson formula helps us to understand the fact that this substance, containing six phenyl radicles, can act as if it had the constitution of triphenylmethyl; for if it be assumed that the molecule is decomposed by halogens in such a way that the single bond between the quinonoid nucleus and the adjacent carbon atom is loosened, then we should have two "triphenylmethyl" radicles set free which would at once react with halogen atoms giving two molecules of triphenylmethyl halide.

The quinonoid formula also makes clear the meaning of the experiments of Gomberg and Cone[1] to which we made reference in a previous section. Let us take for example the case of tri-*p*-bromo-triphenylmethyl chloride—



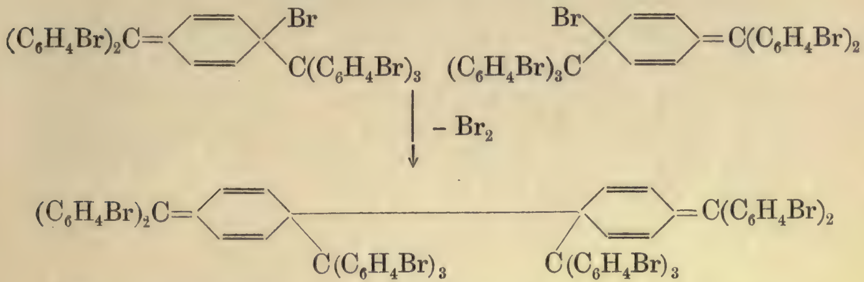
It is clear that, when it is converted into triphenylmethyl by the action of metals, one of the phenyl radicles must become quinonoid; and an examination of the formula of the substance which would be formed if the quinonoid view be correct will show that one of the halogen atoms (marked with an asterisk) should possess the properties of a halogen atom attached to an aliphatic chain rather than those which are shown by halogen atoms bound to aromatic nuclei—



Now, such a halogen atom will be more easily attacked by metals than will be the case with the other bromine atoms in the compound in question; so that we should expect that the action of an excess of, say, silver upon the tri-*p*-bromo-triphenyl-

[1] Gomberg and Cone, *Ber.*, 1906, **39**, 3274.

methane chloride will result in two reactions, the first of which will lead to the elimination of two chlorine atoms, giving rise to the compound whose formula is shown above, while the further action of the silver will remove two bromine atoms from two molecules of this body, the result being the formation of a substance having the constitution shown below—



The results obtained experimentally by Gomberg and Cone proved that one of the phenyl radicles did actually change from the benzenoid to the quinonoid form; but in the view of these experimenters the assumption of this change alone was not sufficient to account fully for the problems which the properties of triphenylmethyl suggest.

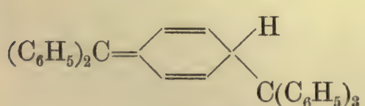
We must now turn to examine the objections which have been brought against the quinonoid view.

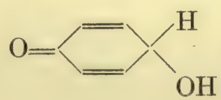
Tschitschibabin[1] pointed out that one of the most speedy and apparently simple reactions which the triphenylmethyl derivatives undergo is the formation of the peroxide—

$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

but that if we are to explain this according to the Jacobson formula we should have to assume an extremely complicated isomeric change as the first step in the process.

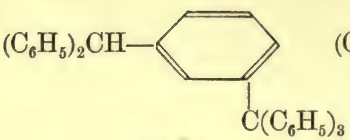
Gomberg and Cone[2] drew attention to the fact that Jacobson makes triphenylmethyl a derivative of a substance analogous to a secondary quinole—





[1] Tschitschibabin, *Ber.*, 1905, **38**, 771.
[2] Gomberg and Cone, *Ber.*, 1905, **38**, 2455.

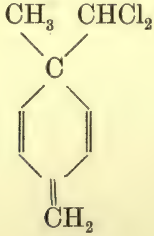
But since secondary quinoles have not yet been proved to be capable of existence, these authors considered doubtful the existence of compounds of the Jacobson type. Furthermore, if we grant the possibility of their existence, it is probable that they will behave like ordinary quinoles, and hence their reactions with acids should resemble to some extent the rearrangements which quinoles undergo under the same conditions. Now in the quinoles, the alkyl group usually wanders to the ortho-position; whence by analogy the substance produced by the action of acids upon triphenylmethyl (Ullmann and Borsum's hydrocarbon) should be represented by the formula (I.) and not by (II.), though Tschitschibabin believed that (II.) was formed. These arguments, as the authors themselves admit, are purely theoretical, and depend largely upon negative evidence.



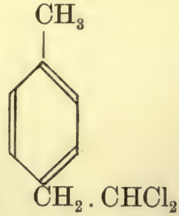
(I.)

(II.)

From a somewhat similar standpoint Auwers[1] has criticized the Jacobson formula. He points out that the para-methylene quinonoid derivatives show such a tendency to revert to the benzenoid structure that in some cases a profound intramolecular change may take place. For example, in the compound (I.) below, the group —$CHCl_2$ wanders from its original position to the atom next the para-carbon atom in order to facilitate the formation of the benzenoid ring (II.) in preference to the quinonoid one—



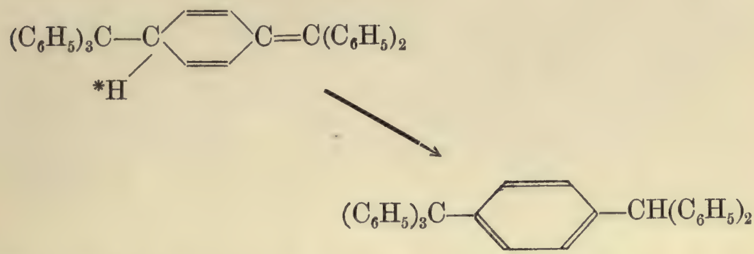
(I.)



(II.)

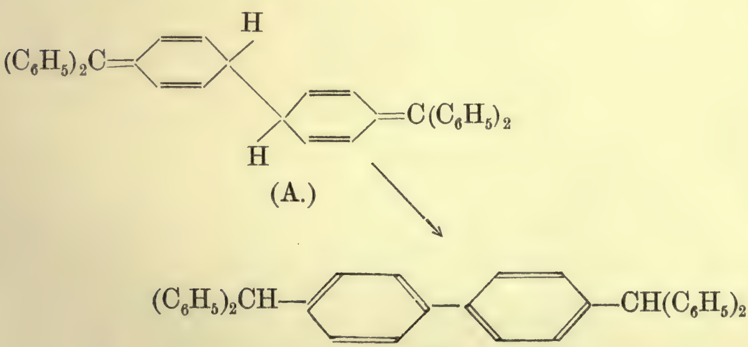
[1] Auwers, *Ber.*, 1907, **40**, 2159.

By analogy, it seems hardly likely that the hydrogen atom marked with an asterisk in the Jacobson formula would remain fixed in its present position when by a similar wandering to the para-carbon atom it could allow the compound to revert to the benzenoid type—



That such a wandering must be possible is shown by the conversion of the Jacobson compound into that of Ullmann and Borsum by the action of acids; but it seems strange that a compound of the Jacobson formula should exist in the free state at all.

Against the Heintschel formula, it has been alleged by Tschitschibabin[1] that it should be easily isomerized into a compound having the structure (B); whereas in practice no such change takes place—



(A.) (B.)

From the foregoing summary it will be seen that the arguments both in favour of and against the quinonoid structure for triphenylmethyl are based very largely upon considerations of

[1] Tschitschibabin, *Ber.*, 1905, **38**, 771.

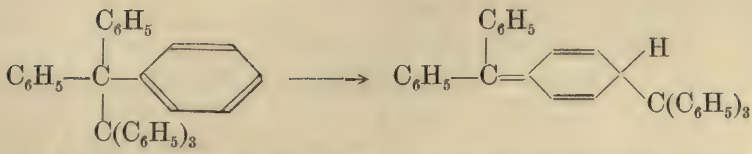
what a compound "ought" to do if it has a structure analogous to some other compound, the latter body being as yet undiscovered in practice. As far as the relevant evidence is concerned, it certainly goes to show that the quinonoid formula is a step in advance of either the triphenylmethyl hypothesis or the hexaphenyl-ethane view, though it fails to account for the molecular weights established by Schlenk.

5. *The Tautomerism Hypothesis.*

We have now exhausted the possibilities of static formulæ to explain the behaviour of triphenylmethyl; and it is evident that the results have not been completely satisfactory. All the three views which we have discussed in the foregoing sections have certain advantages; and each has its own drawbacks. It thus becomes clear that, if we are to make any further progress towards a solution of the problem, we must contrive some means of uniting the advantages of the various formulæ; while at the same time we must endeavour to minimize their weak points. In order to do this it is obvious that we must turn to modern dynamic ideas and represent triphenylmethyl as a series of equilibrium mixtures of isomerides. Gomberg[1] has developed this line of thought; and if his results do not represent the truth, it seems probable that they come very close to it.

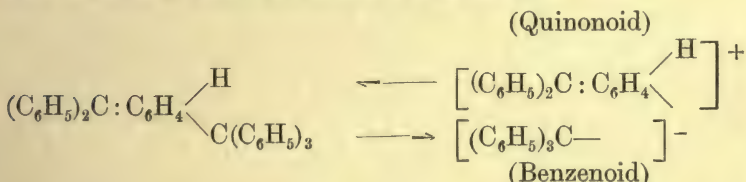
Gomberg's later views took their rise in the fact that there are two varieties of triphenylmethyl which differ from each other in colour: the solid form of the substance is colourless; but in solution this is changed into a yellow compound. Schmidlin[2] states that he has obtained the two forms of the substance in solution. Now, Gomberg assumes in the first place that there are two tautomeric forms of triphenylmethyl, $C_{38}H_{30}$; and in the second place that the radicle triphenylmethyl, $(C_6H_5)_3C$, can exist as such and is also capable of tautomerization. Let us now take up the possible constitution of the solid, colourless modification. This we may suppose to be hexaphenylethane. It is evident that we may assume tautomeric change in this compound, leading us to the following structure:—

[1] Gomberg, *Ber.*, 1907, **40**, 1880.
[2] Schmidlin, *Ber.*, 1908, **41**, 2471.



This alteration of the benzenoid into the quinonoid form would be accompanied by a change of the substance from colourless to yellow; and since all ordinary solvents seem to be capable of yielding yellow solutions of triphenylmethyl, we may assume that this change from the benzenoid to the quinonoid form takes place under the action of most solvents during the process of solution.

We must now go a step further and deal with the behaviour of triphenylmethyl dissolved in a medium of high dissociating power, liquid sulphur dioxide. It has been proved by Walden[1] that a solution of the hydrocarbon in this solvent possesses a fairly high conductivity, and that the molecular conductivity increases with the dilution; in other words, the substance behaves just like an ordinary ionized salt. From this behaviour Gomberg deduces that tautomerization is not the only change which triphenylmethyl undergoes as it is dissolved; but that in addition it is dissociated into two ions which we may represent as below. The anion is supposed to have the benzenoid structure, while the kation is quinonoid—



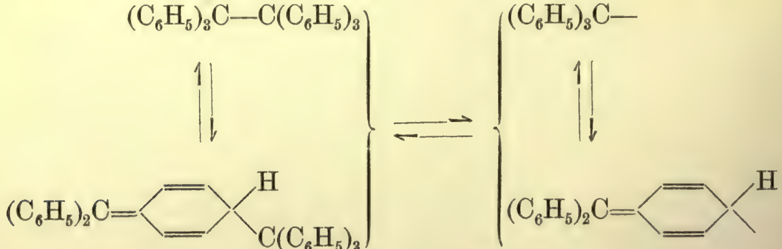
On this view the action of iodine upon triphenylmethyl solutions is explicable. The iodine in solution is supposed to interact with both the anion and the kation, yielding one molecule of benzenoid triphenylmethyl iodide and one molecule in the quinonoid form; but since the latter seems to be incapable of existence in the free state, it is assumed that it undergoes intramolecular change at once and produces a benzenoid molecule. When we turn to the action of oxygen

[1] Walden, *Zeit. phys. Chem.*, 1903, **43**, 443; Gomberg and Cone, *Ber.*, 1904, **37**, 2403.

upon triphenylmethyl in solution, however, we have a somewhat different state of affairs, since only the anion unites with oxygen. (This follows from the fact that the peroxide formed has the benzenoid structure, whereas the action of oxygen upon the quinonoid ion would give rise to a highly complicated product which is not observed among the reaction products.) We are thus led to the further assumption that in the process of peroxide formation the first step is the oxidation of the benzenoid ions; as these are removed from the solution, equilibrium is disturbed; and, in order to re-establish it, some of the quinonoid ions must re-tautomerize into the benzenoid form. They in turn are removed by the oxygen; and the process continues until all the triphenylmethyl is exhausted.

The same tautomerization process can be invoked to explain why triphenylmethyl gives a yellow solution with ethers, esters, and ketones, while the solid double compounds which crystallize out from these solutions are colourless. In this case the benzenoid ions may be assumed to unite with the quadrivalent oxygen of the ethers, etc.; and in order to take their place some of the quinonoid ions are converted into benzenoid ones.

According to Gomberg,[1] then, we can explain all the important properties of triphenylmethyl on the basis of the following hypothesis: (1) tautomerization of hexaphenylethane to a quinonoid substance having the Jacobson formula; (2) partial dissociation of this compound into positive and negative ions in all solvents; (3) mutual interconvertibility of these ions by tautomeric change; and (4) the existence of trivalent carbon atoms giving rise to free radicals. Thus a complete representation of triphenylmethyl's mutations is given by the following scheme:—



[1] Gomberg and Schoeffle, *J. Amer. Chem. Soc.*, 1917, **39**, 1652.

One final piece of evidence may be mentioned here, though its bearing upon the triphenylmethyl problem is an indirect one. If we discard the hypothesis of a quinonoid structure in triphenylmethyl, we are driven back to the idea that the three phenyl radicles, in view of their great amount of residual affinity, affect the fourth valency of the methyl carbon atom and thus allow its trivalence. But if this were so, then three other unsaturated radicles should have the same effect. Now tetranitromethane in certain solvents[1] shows a development of colour similar to that exhibited by triphenylmethyl; and it might be assumed that under these circumstances it was dissociated into a free nitro-group and trinitromethyl:—

$$(NO_2)_3C\,.\,NO_2 \longrightarrow (NO_2)_3C— \quad + \quad —NO_2$$

The fact that the absorption band produced is independent of the nature of the solvent used[2] (provided that any colour is developed at all) seems to support this view.

To test this idea, a series of determinations of the molecular weight of tetranitromethane was carried out[3] in solvents yielding coloured solutions with the solute and also others in which no colour was developed. The method employed was the cryoscopic one. In no case was any sign of dissociation to be found. Solutions of tetranitromethane in acetic acid (where no colour is exhibited) and in naphthalene (which changes to the tint of azobenzene in presence of 2 per cent. of tetranitromethane) gave freezing-point depressions agreeing with the molecular weight of tetranitromethane within 0·2 per cent. Evidently no dissociation occurs in this case, although the three nitro-groups are quite as "negative" and unsaturated as the three phenyl radicles of triphenylmethane are. This seems to show that the explanation of the behaviour of triphenylmethyl must be sought in the nature of the phenyl radicles as distinct from their mere residual affinity.

6. *Thiophene Analogues of Triphenylmethyl.*

Gomberg and Jickling[4] have extended the study of free radicles into the region of the heterocyclic compounds. From

[1] Ostromisslensky, *J. pr. Chem.*, 1911, **84**, 489; Clarke, Macbeth, and Stewart, *Proc.*, 1913, **29**, 161.

[2] Harper and Macbeth, *Trans.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824.

[3] Stewart, unpublished observation.

[4] Gomberg and Jickling, *J. Amer. Chem. Soc.*, 1913, **35**, 446.

α-iodothiophene and benzophenone they prepared, by the Grignard reaction, thienyl-diphenyl carbinol; from which, by the action of hydrogen chloride, they obtained the corresponding chloride. When the last substance is treated in benzene solution with molecular silver or other metals, it exhibits a deep red colour and absorbs oxygen freely. The amount of oxygen absorbed indicates that the following reaction probably takes place:—

$$2\begin{array}{l} C_4H_3S\diagdown \\ C_6H_5{-}C \\ C_6H_5\diagup \end{array} + O_2 = \begin{array}{l} C_4H_3S\diagdown \\ C_6H_5{-}C{-}O{-}O{-}C{-}C_6H_5 \\ C_6H_5\diagup \end{array}\begin{array}{l} \diagup C_4H_3S \\ \\ \diagdown C_6H_5 \end{array}$$

thus bringing the new compound into line with triphenylmethyl in peroxide formation.

This opens up prospects of considerable interest; for the production or non-production of a trithienylmethyl would throw light upon the constitution of triphenylmethyl itself.

CHAPTER XIII.

OTHER ELEMENTS WHICH EXHIBIT ABNORMAL VALENCY.

A. Divalent and Quadrivalent Nitrogen.

1. *Introductory.*

In view of the interest excited by the triphenylmethyl problem from 1900 onwards, it seems strange that no one at that time appears to have thought of examining other compounds which show some structural analogy with hexaphenyl-ethane.

$$(C_6H_5)_3C—C(C_6H_5)_3 \quad (C_6H_5)_2N—N(C_6H_5)_2 \quad C_6H_5—O—O—C_6H_5$$

$$(C_6H_5)_2As—As(C_6H_5)_2 \quad C_6H_5—S—S—C_6H_5$$

In each of the formulæ shown above there is a symmetrical structure; all the formulæ contain a central single bond in the molecule; and the various substances represent the highest possible phenyl-substitution product of their type.

Tetraphenylhydrazine was already known at the time when triphenylmethyl was arousing interest by its peculiar nature; yet no one seems to have been struck by the analogy between it and hexaphenyl-ethane; and it was quite accidentally, in 1906, that the close correspondence between the two series was first brought out in practice.

It has since been shown that, just as the free radicle triphenylmethyl can exist in solution, so can the corresponding diphenylhydrazyl grouping $(C_6H_5)_2N$ appear in the free state; and if carbon is to be considered as a trivalent element in certain circumstances, we cannot deny the possibility of divalent nitrogen derivatives. Between the two series a strong resemblance undoubtedly exists, though the bond N—N is much less readily ruptured than is the case with the single linkage between the central carbon atoms of Gomberg's hydrocarbon.

With regard to the analogous phenyl derivatives of the divalent elements, it is found that experimental evidence points to the possibility of aryl peroxides yielding dissociation products;[1] whilst undoubtedly diphenyl disulphide can, under certain circumstances, give rise to a free radicle. In the following sections of this chapter the behaviour of these compounds will be briefly surveyed.

2. *The Tetra-aryl-hydrazines and their Reactions.*

Tetraphenyl-hydrazine can be prepared either by the action of iodine upon the sodium derivative of diphenylamine[2] or by the oxidation of diphenylamine in an organic solvent by means of lead oxide or potassium permanganate.[3] Obtained by any of these methods, it is a colourless solid melting at 144° C.

As a class the tetra-aryl-hydrazines are stable substances when in the solid state, though they are easily affected by light and are rapidly changed when dissolved in various solvents. Nascent hydrogen converts them with ease into two molecules of the diarylamine from which they were originally produced.

Their most peculiar behaviour is observed when they are treated with acid. In their ordinary form they possess no basic properties; for anhydrous mineral acids give no normal (colourless) salts. On the other hand, when they are acted on by acids, even in organic solvents, they exhibit intense colours,* green, blue, or violet.[4] The coloured derivatives can be isolated in an impure condition; and when they are treated with alkali they regenerate the parent hydrazines. They must therefore be regarded as salt-like addition products of the undecomposed hydrazines.[5]

These coloured products are extremely labile and soon decompose under ordinary conditions, yielding a mixture of

[1] Pummerer and Cherbuliez, *Ber.*, 1914, **47**, 2957.

[2] Chattaway and Ingle, *Trans.*, 1895, **67**, 1090.

[3] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

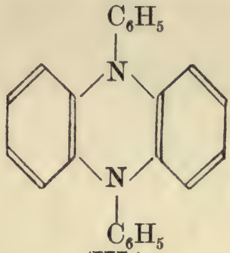
[4] *Ibid.*

[5] Wieland, *Die Hydrazine*, 1913, p. 63.

* Similar colours are obtained with halogens, thionyl chloride, ferric chloride, aluminium chloride, zinc chloride, and the pentachlorides of phosphorus and antimony.

several different compounds.[1] Thus in presence of acids, tetraphenyl-hydrazine gives diphenylamine, *p*-chloro-anilido-triphenylamine (I.), diphenylbenzidine (II.), and a perazine derivative (III.)—

$Cl . C_6H_4 . NH . C_6H_4 . N(C_6H_5)_2$ (I.) $C_6H_5 . NH . C_6H_4 . C_6H_4 . NH . C_6H_5$ (II.)



(III.)

The presence of acids is not essential to ensure the breakdown of the tetra-aryl-hydrazines; for with some of them it is only necessary to heat the substance itself in benzene or toluene solution, whereupon decomposition takes place and follows a course similar to that traced when acids are present, though naturally, with slight variations due to the absence of acidic radicles.[2]

The influence of solvents upon the hydrazines manifests itself in another manner. As has been mentioned, the hydrazines are colourless in the solid state; but when they are dissolved in organic solvents and then heated, a marked colour makes its appearance,* which disappears again if the substance be cooled immediately. Colours also make their appearance when the hydrazines are bombarded with cathode rays and kept cool with liquid air.[3] As soon as the bombardment ceases, the substance reverts to its original colourless condition.†

[1] Wieland, *Annalen*, 1911, **381**, 200; 1912, **392**, 169; *Ber.*, 1907, **40**, 4262; 1908, **41**, 3478.

[2] Wieland and Lecher, *Ber.*, 1912, **45**, 2600.

[3] Wieland, *Annalen*, 1911, **381**, 200.

* Cryoscopic molecular weight determinations prove that the substance $[(CH_3)_2N . C_6H_4]_2N . N[C_6H_4N(CH_3)_2]_2$ is dissociated to an extent of 10 per cent. in benzene solution and 21 per cent. in a solution of nitrobenzene (Wieland, *Ber.*, 1915, **48**, 1078).

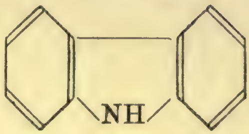
† Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

When treated with nitrogen peroxide in toluene solution at 90° C., tetraphenyl-hydrazine reacts and produces nitroso-diphenylamine (I.); whilst with triphenylmethyl it yields triphenylmethyl-diphenylamine * (II.)—

$$\underset{\text{(I.)}}{(C_6H_5)_2N{-}N:O} \qquad \underset{\text{(II.)}}{(C_6H_5)_3C{-}N(C_6H_5)_2}$$

Alkali metals act on the tetra-aryl-hydrazines with greater or less readiness, producing compounds of the type $R_2:N.Na$, the reaction being similar to that observed in the case of triphenylmethyl.[1]

In conclusion, it must be pointed out that in one case at least the general synthetic method for preparing tetra-aryl-hydrazines breaks down. When carbazole—



is oxidized with the usual reagents, it does not behave like diphenylamine,[2] though it contains the diphenylamine skeleton. Apparently the presence of the pyrrol ring in the compound has some influence upon the reaction; and it is suggested that the extra valency of the nitrogen atom is in this case absorbed by that portion of the molecule.

3. *Wieland's Hypothesis of Divalent Nitrogen.*

In order to explain the reactions described in the foregoing section, Wieland[3] proposes to regard the tetra-alkyl-hydrazines as analogues of the triphenylmethyl series; so that under certain conditions he assumes a depolymerization of the substituted hydrazine which parallels the formation of triphenylmethyl from hexaphenyl-ethane—

$$(C_6H_5)_2N{-}N(C_6H_5)_2 \longrightarrow 2\,(C_6H_5)_2N$$
$$(C_6H_5)_3{\equiv}C{-}C{\equiv}(C_6H_5)_3 \longrightarrow 2\,C(C_6H_5)_3$$

* Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

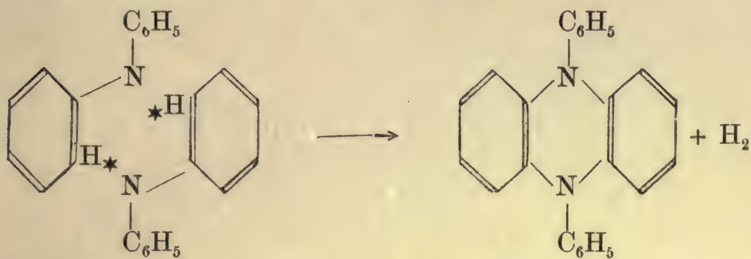
[1] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.

[2] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

[3] Wieland, *Annalen*, 1911, **381**, 200; 1912, **392**, 127; 1913, **401**, 233.

The colours observed when tetraphenyl-hydrazine derivatives are treated with acids or with reagents such as stannic chloride are thus brought into line with those which are obtained in the triphenylcarbinol series under similar conditions.

The formation of a dihydrophenazine derivative and diphenylamine is explained by the mutual oxidation and reduction of four free radicles in the following manner. In the first place, two of them unite with the elimination of two hydrogen atoms (marked with an asterisk) to form diphenyl-dihydrophenazine—



These two hydrogen atoms, thus set free, then reduce the two other free radicles to form two molecules of diphenylamine—

$$2\,\begin{matrix}C_6H_5\diagdown \\ \\ C_6H_5\diagup\end{matrix}\!N + H_2 \longrightarrow 2\,\begin{matrix}C_6H_5\diagdown \\ \\ C_6H_5\diagup\end{matrix}\!NH$$

The two steps in the process may be inverted without altering the argument.

The production of nitroso-diphenylamine, on this hypothesis may be represented thus—

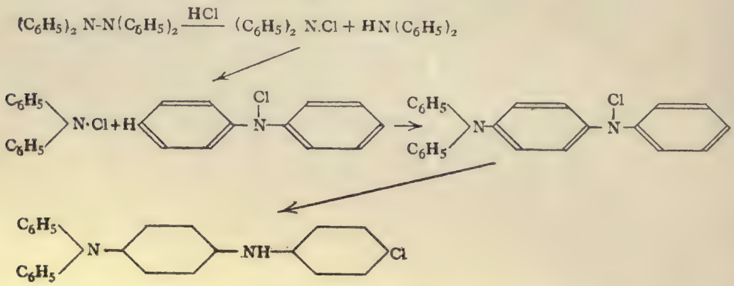
$$\begin{array}{ccccccc}
 C_6H_5 & & & & C_6H_5 & & C_6H_5 \\
 | & & & & | & & | \\
C_6H_5{-}N & & NO & & C_6H_5{-}N \quad NO & & C_6H_5{-}N{-}N{:}O \\
 | & + & | & \longrightarrow & & \longrightarrow & \\
C_6H_5{-}N & & NO & & C_6H_5{-}N \quad NO & & C_6H_5{-}N{-}N{:}O \\
 | & & & & | & & | \\
 C_6H_5 & & & & C_6H_5 & & C_6H_5
\end{array}$$

and the reaction with triphenylmethyl is simply a union of the two free radicles to form triphenylmethyl-diphenylamine—

$$(C_6H_5)_3C + N(C_6H_5)_2 \longrightarrow (C_6H_5)_3C{-}N(C_6H_5)_2$$

To account for the formation of *p*-chloro-anilido-triphenylamine, Wieland assumes that the first action of acids upon

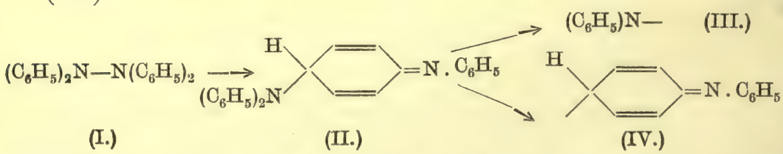
tetraphenyl-hydrazine is to decompose it into one molecule of diphenylamine and one molecule of chloro-diphenylamine, two molecules of which then interact as shown below—



4. *Stewart's Application of the Quinonoid Hypothesis.*

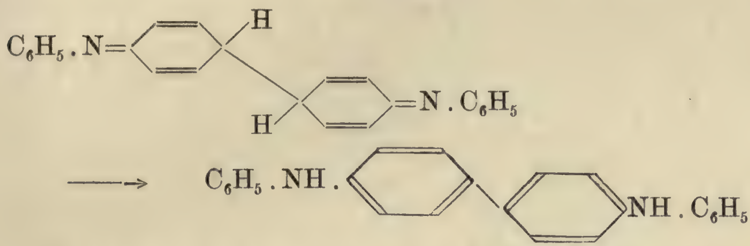
The parallelism between the tetraphenyl-hydrazine derivatives and the triphenylmethyl group is so close that it seems not unwarrantable to extend to the former the ideas which have been used to account for the behaviour of the trivalent carbon compounds.

In the triphenylmethyl group, it was assumed that hexaphenyl-ethane was capable of intramolecular change resulting in a quinonoid structure. An analogous change in tetraphenyl-hydrazine would result in the formation of a compound of the type (II.) which, if we follow out the parallel, would dissociate into a benzenoid portion (III.) and a quinonoid part (IV.)—

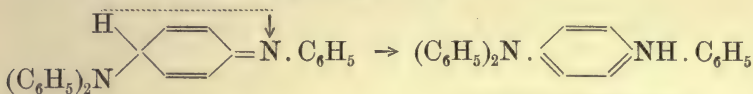


The presence of the quinonoid structure here would account for the appearance of colour when colourless tetraphenylhydrazine is heated in solution, and also for the readiness with which the substance is affected by light.

To account for the production of diphenylbenzidine from the hydrazine, it is only necessary to assume that two molecules of (IV.) join together and then rearrange themselves into the benzenoid form—



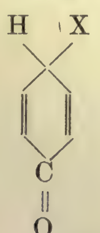
To explain the production of *p*-chloro-anilido-triphenylamine, it may be assumed that in acid solution the radicle $(C_6H_5)_2N$ is attacked by a chlorine ion, giving chloro-diphenylamine, after which the reactions would take place according to Wieland's suggestion. The occurrence of the parent substance, anilido-triphenylamine, which is noticed when tetraphenyl-hydrazine is heated in benzene solution, can be even more simply explained by a wandering of a hydrogen atom; thus recalling the formation of Ullmann and Borsum's hydrocarbon in the case of triphenylmethyl—



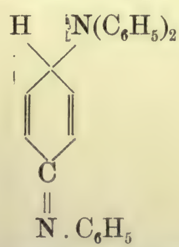
Anilido-triphenylamine.

The interaction with triphenylmethyl and with nitrogen peroxide is easily accounted for by assuming that these two reagents combine directly with the free benzenoid radicles (III.).

In order to make clear the formation of the perazine derivative it must be pointed out that along with one molecule of this substance, the reaction gives rise simultaneously to two molecules of diphenylamine. Now an examination of the quinonoid structure proposed for tetraphenyl-hydrazine suggests a resemblance to the quinole constitution—

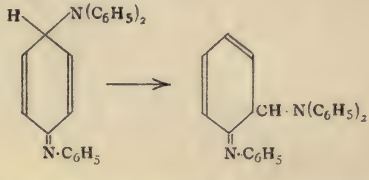


Quinole.

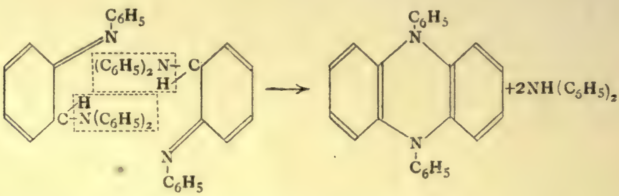


Tetraphenyl-hydrazine.

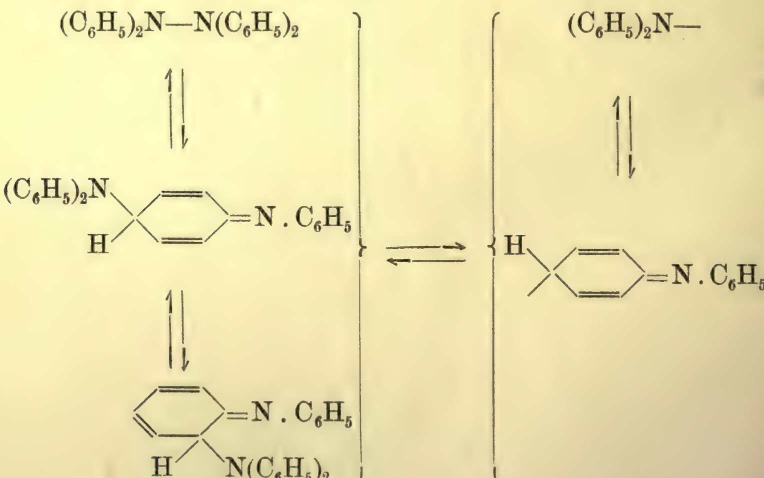
and just as some quinoles exhibit a wandering of the group X to the nucleus, so we may assume a similar wandering to take place in the case of tetraphenyl-hydrazine, giving rise to a compound of the following structure—



Two molecules of this would combine directly to produce a perazine and at the same time eliminate two molecules of diphenylamine (as shown by the dotted line) for each molecule of perazine produced—



Thus in order to account satisfactorily for the various reactions of tetraphenyl-hydrazine, it is necessary to assume the following series of equilibria :—



5. *A Derivative Containing Quadrivalent Nitrogen.*

The oxidation of diphenyl-hydroxylamine with silver hydroxide yields a compound[1] which appears to have the formula shown below—

$$(C_6H_5)_2:N.OH \xrightarrow{Ag_2O} (C_6H_5)_2:N:O$$

Owing to its analogy in structure with nitrogen peroxide, this substance is termed diphenyl-nitrogen oxide. It is a crystalline compound, deep red in tint; and its vapour resembles that of nitrogen peroxide. It liberates iodine from potassium iodide—

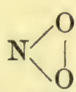
$$(C_6H_5)_2:N:O + 3HI = (C_6H_5)_2:NH + 3I + H_2O$$

With bromine it gives a halogen derivative of diphenylamine containing two bromine atoms attached to one phenyl nucleus and one bromine atom in the other. With nitrogen peroxide and triphenylmethyl it reacts readily. Concentrated mineral acids react with almost explosive violence upon the new compound.

The molecular weight determined cryoscopically in benzene corresponds to the monomolecular formula; and this apparently remains unaltered even in a mixture of ether and carbon dioxide, for at − 60° C. the substance can be recrystallized from ether and still retain its red colour.

One point of interest in connection with the compound is that its discovery throws considerable doubt upon a structure suggested for nitrogen peroxide: for it is clear that diphenyl-nitrogen oxide resembles nitrogen oxide closely; and this tends to support the formula (II.) as against (III.)

$(C_6H_5)_2{=}N{=}O$ (I.) $O{=}N{=}O$ (II.)



(III.)

The formation of $Br_3C_6H_2$—NH—C_6H_4Br by the action of bromine upon the substance may point to the existence of a quinonoid grouping in the molecule; and it is possible that the case may be one of trivalent carbon instead of an example of quadrivalent nitrogen. Too little is known of the subject at present to make it worth while to speculate further.

[1] Wieland and Offenbächer, *Ber.*, 1914, **46**, 2111.

B. Derivatives of Monovalent Sulphur.

The oxidation of phenyl mercaptan yields phenyl disulphide,

$$C_6H_5—S—S—C_6H_5$$

This substance in the solid state is colourless, but when it is dissolved in any indifferent solvent, the solution shows a faint yellow tinge, and the colour is intensified by raising the temperature. On cooling, the solution regains its original tint. This change in colour cannot be attributed to dissociation, according to Lecher,[1] since the solutions do not deviate from Beer's Law when examined in a colorimeter; so that the case is not parallel to that of triphenylmethyl in this respect.

Further, in the case of *p*-dimethylanilido-disulphide—

$$(CH_3)_2N—C_6H_4—S—S—C_6H_4—N(CH_3)_2$$

an analogous colour change is observed when the solid substance is heated and cooled.

To explain these phenomena, Lecher suggests that the bond between the sulphur atoms is not broken but is merely weakened; and that the weakening of the valency and the development of colour are parallel changes.

Evidence of this weakening of the bond between the sulphur atoms was sought for in various reactions. For example, at ordinary temperatures or even at 80° C. sodium has little effect upon phenyl disulphide; but at 125° C. it reacts to produce sodium mercaptide—

$$C_6H_5—S—S—C_6H_5 + 2Na = 2C_6H_5—S—Na$$

The weakness of the bond between the sulphur atoms is also indicated by the interaction of *p*-dimethylanilido-disulphide and triphenylmethyl, which gives rise to 1-dimethylamido-phenyl-4-triphenylmethyl disulphide—

$$(CH_3)_2N . C_6H_4—S—S—C_6H_4 . N(CH_3)_2 + 2(C_6H_5)_3C$$
$$= 2(CH_3)_2N . C_6H_4 . S . C(C_6H_5)_3$$

These reactions suggest that under certain conditions it might be possible to obtain derivatives of monovalent sulphur; and though no actual isolation of such compounds has yet been achieved, their existence has been rendered probable by the following evidence.[2] Phenyl-triphenylmethyl sulphide

[1] Lecher, *Ber.*, 1915, **48**, 524. [2] *Ibid.*

can be obtained by the action of triphenyl-chloro-methane upon sodium phenyl mercaptide—

$$C_6H_5.S.Na + Cl.C(C_6H_5)_3 = C_6H_5.S.C(C_6H_5)_3 + NaCl$$

Now this sulphide becomes strongly yellow when heated in ethyl benzoate solution; and an examination of the spectrum proves that triphenylmethyl is present. By shaking the solution in the air, the triphenylmethyl is oxidized, the solution becomes colourless; and by further shaking in an indifferent atmosphere the yellow colour of triphenylmethyl reappears owing to a further decomposition of sulphide. The only way in which this reaction can reasonably be expressed is as follows—

$$C_6H_5—S—C(C_6H_5)_3 = C_6H_5.S + C(C_6H_5)_3$$

Further evidence [1] is found in the examination of mercury phenyl mercaptide, $C_6H_5.S.Hg.S.C_6H_5$. It was observed by Dreher and Otto,[2] that this body, when heated, breaks up into mercury and phenyl disulphide; and this suggests that heat loosens the bond between the sulphur and mercury atoms. On Lecher's view, the weakening of the valency force ought to be accompanied by a development of colour as the temperature rises. This actually proves to be the case. Whether dry or in solution, the mercaptide is colourless at ordinary temperatures but becomes yellow when heated, though no mercury separates from it under the experimental conditions employed.

Lecher suggests that the Dreher-Otto reaction is a reversible one which may take one of the two following courses :—

$$\text{(I.)}\quad (C_6H_5.S)_2Hg \rightleftharpoons C_6H_5S.S.C_6H_5 + Hg$$

$$\text{(II.)}\quad (C_6H_5.S)_2Hg \rightleftharpoons 2C_6H_5.S + Hg$$

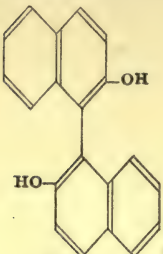
$$2C_6H_5.S \rightleftharpoons C_6H_5.S.S.C_6H_5$$

If it can be proved that the reaction includes the two equilibria shown in (II.), the existence of monovalent sulphur would be established; but at present the subject is not beyond dispute; and we must wait for further evidence before classing monovalent sulphur compounds along with the better-established cases of trivalent carbon and divalent nitrogen.

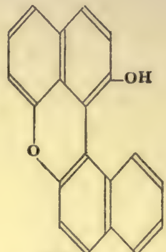
[1] Lecher, *Ber.*, 1915, **48**, 1425.
[2] Dreher and Otto, *Annalen*, 1870, **154**, 178.

C. A Derivative of Monovalent Oxygen.

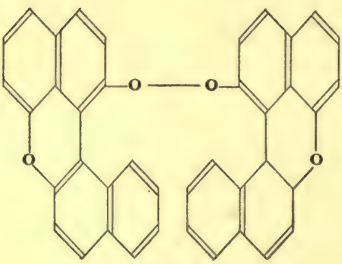
When β-dinaphthol (I.) is oxidized with silver hydroxide, it yields a substance termed hydroxy-naphthylene oxide, to which the formula (II.) is ascribed. By treating this with potassium ferricyanide or indigo white, dehydroxy-dinaphthylene oxide is formed, which is supposed to have the structure (III.) or (III.*a*). This body, when dissolved in various solvents, shows colour phenomena akin to those observed in the triphenylmethyl series; and, partly on this ground, it is assumed to dissociate into radicles[1] which have either of the structures (IV.) and (V.).



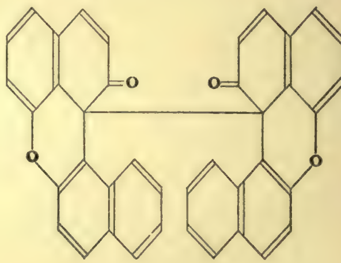
(I)



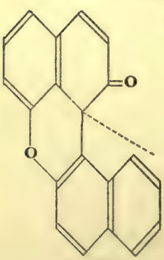
(II)



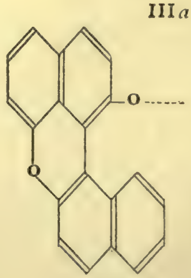
III



III*a*



(IV)



(V)

[1] Pummerer and Frankfurter, *Ber.*, 1914, **46**, 1472; compare Pummerer and Cherbuliez, *ibid.*, 2957.

The supposed free radicle reacts readily with oxygen (though less rapidly than triphenylmethyl) forming an ochre peroxide. Iodine also acts upon it more slowly than might have been anticipated. Hydrochloric acid decomposes it. Triphenylmethyl, cyclopentadiene, and pinene add themselves on to the radicle. Nitrogen peroxide forms an additive compound in ethereal or benzene solution but does not attack the radicle to any extent in chloroform solution. When the substance is boiled in benzene solution it undergoes decomposition, yielding hydroxy-dinaphthylene oxide and dinaphthylene dioxide.

It will be seen from the above data that the compound is extremely complicated; its reactions have not yet been fully studied; and it may be well to refrain from laying too much stress upon its structure till its properties have been more thoroughly investigated.

D. Monovalent Mercury.

If a liquid ammonia solution of methyl mercury chloride, $CH_3 . Hg . Cl$, is electrolyzed with a small cathode, a highly attenuated opaque mass collects around the cathode.[1] When the mass is collected and allowed to warm up to near ordinary temperature it suddenly undergoes decomposition with the evolution of heat. The reaction appears to correspond to the following equation :—

$$2CH_3 . Hg = Hg + Hg(CH_3)_2$$

Other compounds containing other alkyl radicles and acidic groups behave similarly.

The material is black, like a finely divided metal ; and it is a good conductor of electricity. It does not amalgamate with mercury to any marked extent.

It is suggested by Kraus that this compound contains monovalent mercury ; and this is possibly the case. On the other hand, it is not improbable that it is actually $CH_3 . Hg . Hg . CH_3$; which might be formed at the small cathode just as persulphates are formed from sulphates under similar conditions at the anode. Further research will probably decide which of these views is correct.

[1] Kraus, *J. Amer. Chem. Soc.*, 1913, **35**, 1732.

E. Conclusion.

The nature and behaviour of the triaryl-methyls and the tetra-aryl-hydrazines suggest problems which bring us to the very bases upon which rest our modern views of structural chemistry. Once the idea of "free radicles" is accepted, our long-tried dogma of the quadrivalence of carbon comes into the scales for a final test. It is doubtful if we shall throw over the older ideas suddenly. Already there is a tendency to look for a new conception of valency, a tendency which is displayed in the modern theories of partial valency and residual affinity: but these views are at present disjointed; and there is little sign of their being welded into a connected whole which will carry conviction by its clarity and flexibility.

In the meantime, it seems desirable that further examples of these peculiar compounds should be examined; so that as wide a basis as possible may be used for generalization. Attempts[1] have been made to prepare analogues of tetraphenyl-hydrazine in the arsenic group, such as

$$(C_6H_5)_2As—As(C_6H_5)_2$$

but, up to the present, no actual proof of the dissociation of such substances into free radicles has been obtained. Possibly the temperature employed was not sufficiently high * to produce a rupture between the arsenic atoms. Further experiments may prove more successful; or fruitful subjects for investigation might be found in the analogous compounds derived from phosphorus, antimony, or bismuth. The analogues of carbon (silicon, tin, and lead) also suggest themselves for research purposes; for it can hardly be assumed that carbon, sulphur, and nitrogen are the only atoms capable of showing this peculiarity.

[1] Schlenk, *Annalen*, 1912, **394**, 216.

* A solution of the substance in boiling benzene was used.

CHAPTER XIV.

MODERN FORMULÆ AND THEIR FAILINGS.

An unbiassed survey of the fields covered by organic chemistry cannot fail to reveal to any critical mind the fact that our structural formulæ are becoming less and less able to cope with the strain which modern research is placing upon them. It is true that for work-a-day purposes they still answer admirably; and from the point of view of teaching it is doubtful if anything better could be devised. But when we go into the matter beyond the mere surface, things are not so satisfactory as they may appear to the superficial observer. In the present chapter an attempt will be made to indicate briefly some points in the problem.

In the first place, it will be well to inquire as to the exact nature of our present-day formulæ. According to Kekulé,[1] structural formulæ were "decomposition" formulæ:—

"Rational formulæ are decomposition formulæ, and in the present state of chemical science can be nothing more. These formulæ give us pictures of the chemical nature of substances; because the manner of writing them indicates the atomic groups which remain unattacked in certain reactions. . . . Every formula which expresses definite metamorphoses of a compound is *rational*; that one of the different rational formulæ is the *most rational*, which expresses the greatest number of these metamorphoses."

Couper,[2] on the other hand, put the case as follows:—

"Gerhardt . . . is led to think it necessary to restrict chemical science to the arrangement of bodies according to their decompositions, and to deny the possibility of our comprehending their molecular constitution. Can such a view

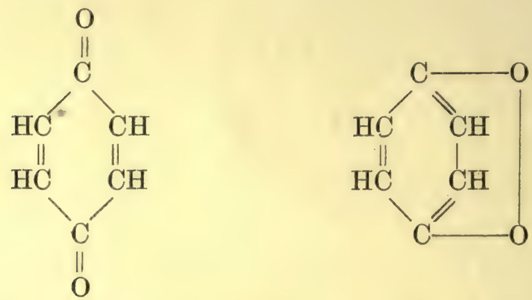
[1] Kekulé, *Annalen*, 1858, **106**, 149.

[2] Couper, *Phil. Mag.*, 1858, IV., **16**, 107

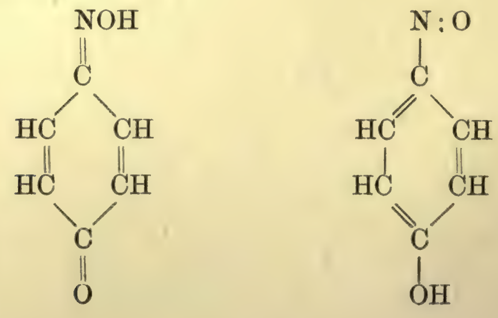
tend to the advancement of science? Would it not be only rational, in accepting this veto, to renounce chemical research altogether?"

Thus, on the one side, we have Kekulé maintaining that graphic formulæ are mere shorthand symbols by means of which we can easily and compactly express the results of our chemical experiments; whilst, on the other side, Couper claims that these ciphers give us the key to the actual mode of linkage of the atoms within the molecule. Let us take each of these views in turn and see how far they can be brought into agreement with modern conditions.

Regarded as pure reaction-formulæ, it must be admitted that our present symbols fail at too many points for our intellectual satisfaction. If we take the case of quinone as an example, we find that its formula is written in either of two ways—

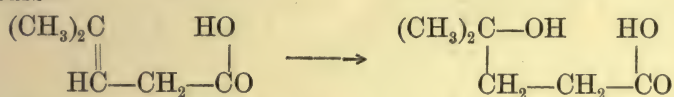


each of which is a representation of its method of reacting with a certain reagent. But neither of these formulæ allows us to foresee the fact that quinone monoxime will react as if it were nitroso-phenol—



The number of facts of this type which have accumulated in recent years is considerable, and the result of this increase in knowledge has been remarkable. Instead of attempting to bring their formulæ into harmony with the facts, organic chemists have been content to drag behind them a lengthening chain of implications, which they read into a formula; *e.g.*, in the case of acetone and ethyl acetate we do not distinguish in our formulæ between the two carbonyl groups, but we mentally interpret the two symbols differently. Thus, at the present time, it is quite conceivable that a student may be well acquainted with the meaning of all the ordinary chemical symbols, but may be hopelessly at sea with regard to the behaviour of a given compound; though to a more experienced chemist this is implicitly expressed in the formula which misleads the beginner.

A concrete example will serve to bring out the amount of unexpressed material which we read into the ordinary formula. Let us consider the reactions of the unsaturated monobasic acids in presence of dilute sulphuric acid. In the first place, we assume that an addition of water to the double bond occurs—



Now, we know from general experience that when one hydroxyl group lies in the 1, 6-position to another in the same chain, water is usually eliminated with ease; so we should deduce that the next step in the process would be such an abstraction of a water molecule—

The formation of this compound is actually what does take place, so that in this case our implications are justified; but let us apply the same series of ideas to another instance. Take the case of vinyl-acetic acid (I.), which contains the double bond in exactly the same position as in the other substance. Applying our experience as before, we should deduce that the final product on heating with dilute sulphuric acid would be the lactone (II.). In practice no such substance is formed, the product being the new unsaturated acid (III.).

$$CH_2:CH.CH_2.COOH \qquad \begin{array}{l} CH_2\text{———}O \\ | \qquad\qquad | \\ CH_2.CH_2.CO \end{array} \qquad CH_3.CH:CH.COOH$$

(I.) (II.) (III.)

But this does not bring us to the end of the possible reactions of this class of substances; for if we take the case in which two methyl groups are attached to a different carbon atom we find that the reaction follows yet another course—

$$CH_2:CH.C(CH_3)_2.COOH \longrightarrow CH_3.CHOH.C(CH_3)_2.COOH \longrightarrow CH_3.CH:C(CH_3)_2 + CO_2 + H_2O$$

Thus, our formulæ have ceased to be true reaction formulæ, and may merely serve to mislead us if we attempt to draw any general conclusions from them.

Let us now turn to Couper's view of formulæ, *viz.*, that they are to be regarded as true representations of the intimate structure of molecules. Here we appear to be upon safer ground; but again we meet with drawbacks. If a formula represents the actual mode of linkage of the atoms in a molecule, how can we be certain of our results when we apply chemical reagents to the compound? Quinone, when treated with hydroxylamine, behaves as if it contained a carbonyl radicle; but if we employ phosphorus pentachloride as our reagent it acts as if quinone contained a benzene nucleus, since *p*-dichlorobenzene results. In this case, what is the true structure of quinone? If it be regarded as an equilibrium mixture of two compounds or as existing in two vibration-phases, what becomes of our "intimate structure of the molecule"?

Evidently, from Couper's point of view, the outside reagent is a disturbing factor not allowed for in our formulæ. An example is furnished by the action of hydroxylamine upon mesityl oxide.[1] If the action is allowed to take place in a methyl alcoholic solution in presence of sodium methylate, the chief

[1] Harries and Lellmann, *Ber.*, 1897, **30**, 230, 2726; Harries and Jablonski, *ibid.*, 1898, **31**, 1371; Harries, *Annalen*, 1904, **330**, 191.

product is the substance formed by the addition of hydroxylamine to the double bond—

$$\begin{array}{l}(CH_3)_2\underset{\displaystyle\underset{NH\,.\,OH}{|}}{C}\,.\,CH_2\,.\,CO\,.\,CH_3\end{array}$$

But if, on the other hand, we take hydroxylamine hydrochloride and after exactly neutralizing it with sodium carbonate allow it to act upon an alcoholic solution of mesityl oxide, we get the usual carbonyl group reaction, and mesityl oxime is formed—

$$(CH_3)_2C : CH\,.\,C(NOH)\,.\,CH_3$$

Thus in *alkaline* solution the ethylenic bond is stimulated into activity, while in *neutral* solution the carbonyl radicle appears the more reactive of the two.

From this it becomes clear that in order to ascertain the true "intimate structure of the molecule" we must find some way of determining it apart from extraneous materials. How is this possible?

The recent developments in the study of physical properties of compounds indicate a means whereby the constitution of a body might be guessed without the necessity of applying disturbing reagents to it. At present our methods are not sufficiently advanced to permit us to establish molecular structure definitely by physical means alone; but even to-day we can accomplish a good deal with the help of absorption spectra, magnetic rotation, refractive index, magnetic susceptibility, electric absorption, optical rotatory power and dispersion; and there seems to be little reason to despair of further progress.

It is at this point that we encounter the difficulty which has been responsible for wrecking a considerable amount of work in recent years. On the one hand, as we have seen, stand our "chemical" formulæ which give us—incompletely enough, it must be confessed—a picture of the reactions of substances. On the other side, physical methods are showing us glimpses of the "intimate structure of molecules". Now a great mistake appears to have been made in assuming that both these things could be expressed by the same formulæ. Our old reaction-formulæ, though unable to cope with the difficulties in their own special field, have been imported willy-nilly into the problem of molecular structure, because

we had nothing better to utilize there. The result has been something like the state of affairs which would reign in arithmetic if we insisted on using a mixture of Roman and Arabic notations in our calculations.

It is evident that progress along these lines will be slow. What is required is that those investigators who concern themselves with physical properties should invent special symbols * to express their results and should thus be freed from the implications which cling to the ordinary formulæ. Then, at a later stage, it may be possible, with increased knowledge, to harmonize the two symbolical systems and produce a combined notation which will include the valuable parts of each.

Unfortunately, there seems little doubt that this suggestion will be ignored. Conservatism is ingrained in most scientific minds; and the struggle which new ideas have before them is generally severe.†

We must now turn to another region wherein our modern formulæ are failing to meet the demands made upon them. When we examine the matter closely, we find that the foundations of theoretical organic chemistry are a series of labels by means of which we endeavour to conceal our ignorance of the fundamental phenomena of the subject. Of these labels, none is used more indefinitely and at random than the word "Unsaturation". What do we mean by an unsaturated compound? It may be defined as a molecule which, without total disruption of its original structure, is capable of uniting with one or more fresh molecules.

Now when we consider unsaturation in its broadest aspects, it is evident that what we call unsaturation is a specific and not a general property. We represent the unsaturation of an ethylenic linkage and of a carbonyl radicle by the same symbol, a double bond; and as far as the action of nascent hydrogen is concerned, this is quite accurate, for both the ethylenic linkage and the carbonyl group will attach to themselves two atoms of hydrogen. But when we use bromine instead of hydrogen, we

* The electronic symbols suggested by Nelson and Falk represent something akin to what is intended; though in their present form they cling too closely to ordinary formulæ.

† An amusing example of this is to be found in Kolbe's review of van't Hoff's theories on their first publication.

find that only the ethylenic linkage reacts; for the carbonyl radicle remains unaffected by the reagent.

Thus we cannot say definitely that the ethylenic linkage is more or less active than the carbonyl bond; for the matter is influenced in different ways by the reagent employed, the solvent used, and the relative position of the two double bonds in the molecule. In other words, "unsaturation" is not a definite, measurable thing which we can predict in any case from the behaviour of the "unsaturated" substance in other circumstances; it is rather something kinetic, something which is extremely sensitive to external forces, and which in its turn can play a part in influencing the chemical action of groups which it does not apparently affect directly.

As an example of this latter property we may quote the case of the Vorländer Rule.[1] Vorländer has pointed out that we can consider both acids and alcohols as derived from water by substitution. In the case of acetic acid we substitute an acetyl group for one of the hydrogen atoms of water, while ethyl alcohol is formed from water by the substitution of an ethyl group for a hydrogen atom—

$$H{-}OH \qquad CH_3 . CH_2{-}OH \qquad CH_3 . CO{-}OH$$

When we examine the chemical behaviour of the hydrogen atom in each case, we find that in the acids it has a much greater activity than in the alcohols. The origin of this difference obviously lies in the difference between the acyl and alkyl groups to which the hydroxyl radicle is united. The question is commonly dealt with by labelling the acyl group "electro-negative," and treating the label as an explanation. But, as Vorländer pointed out, this case is only one example of a general rule. If we represent non-metallic elements by E, and write down the following series :—

$$\overset{1}{H} . \overset{2}{E} . \overset{3}{E} : \overset{4}{E}$$

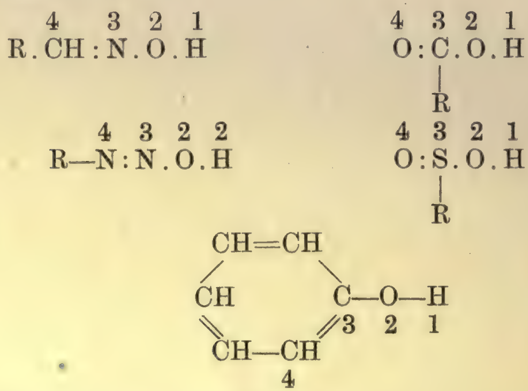
$$\overset{1}{H} . \overset{2}{E} : \overset{3}{E}$$

$$\overset{1}{H} . \overset{2}{E} . \overset{3}{E} . \overset{4}{E} : \overset{5}{E}$$

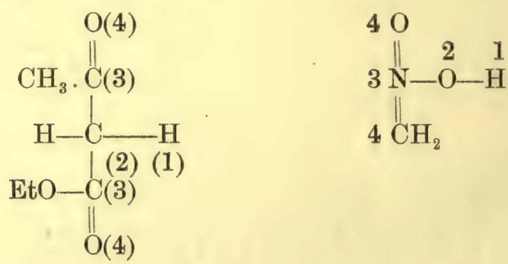
we shall find that the hydrogen atom in the first line has a

[1] Vorländer, *Ber.*, 1901, **34**, 1633.

greater reactivity than those in the second and third lines; in the first case the double bond between two E atoms lies in the 3:4 position to the labile hydrogen atom, while, where the double bonds are in the 2:3 or 4:5 positions the hydrogen atom is not specially active. For example, the labile hydrogen atoms in oximes, acids, phenols, diazo-compounds, and sulphinic acids are all situated as in the first type with respect to the double bond—

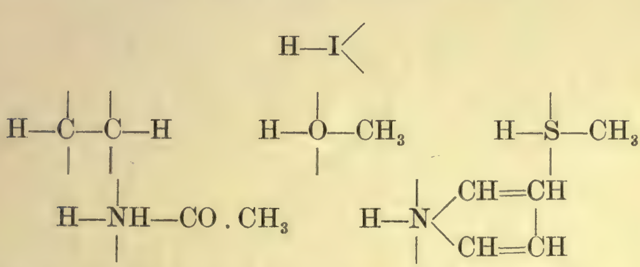


In aceto-acetic ester and nitro-methane the hydrogen atoms are doubly influenced—



Further, when an acid or a ketone is brominated, the halogen atom enters the nucleus in the position required by this rule, *i.e.*, it replaces the hydrogen atom in the *a*-position to the carbonyl group—

There seems to be another influence at work in the case of acidic hydrogen atoms; and as the matter appears to have escaped notice hitherto, it may be well to call attention to it in this connection.[1] An examination of the formulæ of those substances which are capable of yielding metallic derivatives by direct displacement of a hydrogen atom will show that the atom to which the labile hydrogen is attached is capable of exerting a valency higher than that which it exhibits in the acidic compound. For example, in the following substances the oxygen and sulphur atoms are divalent, while both oxygen and sulphur are capable of acting as quadrivalent elements; carbon in acetylene acts as a divalent atom, though its maximum valency is four; the nitrogen atoms shown below are trivalent, but nitrogen can act as a pentad; iodine can act either as a mono- or a trivalent element. The formulæ are written with lines to show the extra valencies—



It will be seen that this is of more general application than the Vorländer Rule, for it holds in the case of substances such as ethylates, whose formation takes place though there is no double bond in the molecule such as is required by Vorländer's view. In fact, the structure demanded by the Voländer Rule is merely a reinforcing influence upon the lability of the hydrogen which already exists owing to the presence of the atom capable of showing a rise in valency.

We must now turn to another point of view. Hitherto we have regarded unsaturation from the standpoint of addition reactions, but we may now extend this a little. Suppose that we have two isomeric substances, each capable of taking up four bromine atoms, are these two bodies equally saturated or are they not? The question of unsaturation thus resolves

[1] Smiles, *Trans. Chem. Soc.*, 1900, **77**, 160.

itself into one of stability. We cannot distinguish between the bodies by the *amount* of bromine they take up, so we seek some other criterion. Now, in the case of two substances, one of which has a pair of conjugated double bonds, while in the other the bonds are not so related, the second substance takes up the four bromine atoms at once, but the first one takes them up two by two. The action is thus more precipitate in the second instance, and we should be tempted to consider the first substance as the less unsaturated of the two. In fact, as Thiele put it, the conjugated double bonds partially saturate one another.

Further, when an unsaturated acid is brought into conditions which allow it to undergo isomeric change, it is almost always converted into the form which contains the ethylenic bond conjugated with that of the carboxyl group. Evidently, then, this grouping must be the most exothermic, and therefore the most saturated.

We may now sum up, as far as possible, the various points which we have treated in the foregoing pages. We have shown, in the first place, that unsaturation is not an intrinsic property of any molecule. It depends largely upon the nature of the outside reagent; in order to have "unsaturation" we must have two substances, each specially fitted to interact with the other. In fact, the addition reactions of organic chemistry appear to be an extreme case of the ordinary reactions of salt formation, such as takes place in the case of ammonia and acid. Secondly, the influence of the other (non-reacting) parts of the molecule may play a very considerable part in any addition reaction, so that we cannot ascribe the same meaning to every double bond that we write down. For example, since the ethylenic bond in maleic acid refuses to react with hydroxylamine, it must be chemically quite different from that in mesityl oxide which reacts readily in alkaline solution. Thirdly, just as unsaturation can be influenced by neighbouring unsaturations, it can in turn exert an influence upon groups of atoms in its vicinity. And, finally, if we have a series of unsaturations in a molecule they can be made to rearrange themselves to form a more stable system.

It is especially in this region of unsaturation that we find the limitations of our structural formulæ most clearly marked.

When we write a double bond between two atoms, we do not always mean the same thing. The double bonds in the cases of diphenyl-ethylene, ethylene, and fulvene certainly do not resemble one another chemically: in the first case the double bond is not attacked by bromine, which is taken up easily by the double bond of ethylene; but while the fulvene series are oxidized by air, ethylenic substances are not. Thus we have an increase in unsaturation (or reactivity as regards bromine and oxygen) as we go from diphenyl-ethylene through ethylene to the fulvenes; yet we symbolize all three unions between the carbon atoms of the double bonds in exactly the same way. It is perfectly evident that the amount of reactivity is different in these three cases, and therefore the "chemical affinity," which gives rise to the reactions, must be different also.

But it is not only in the case of the double bond that we can trace this alteration in value of valencies; we can discover it in the case of single bonds as well. It is well known that in bromo-benzene, the bromine atom is held to the carbon atom of the nucleus more firmly than is the case in aliphatic bromine derivatives. But if we nitrate the benzene ring, the bromine in the aromatic bromine derivative becomes as labile as that in the aliphatic one. This increase in reactivity can be due only to some change in the force which holds together the carbon and bromine atoms; in other words, the "valency-force" uniting bromine to carbon is stronger in bromobenzene than in nitro-bromobenzene.* Flürscheim [1] has carried out some experiments by means of which he showed that this variation in the value of the single bond is quite a general property.

It may be supposed by some that if we accept these ideas we shall be taking a retrograde step, and plunging ourselves into a web of inconsistencies; but surely it is not so! At the time of Frankland, chemists had not acquired those ideas of chemical structure which we now possess, and which we cannot

* When the above paragraph was written in 1908, I was under the impression that this had long been common knowledge. Dr. Flürscheim desires me to mention, however, that he published a paper on the point in 1906 (*Ber.*, **39**, 2016).—A. W. S.

[1] Flürscheim, *J. pr. Chem.*, II., 1902, **66**, 329; see also Werner, *Ber.*, 1906, **39**, 1278.

abandon without having something better to take their place; consequently, it was necessary for the science to go through a stage in which valency was regarded as a fixed, unalterable force; without this guiding principle the work of the last forty years would have been impossible.[1] But we have now reached a point from which we can look back and enlarge our views without running the risk of losing hold of what we have acquired. Instead of regarding a "bond" as a fixed unit, we can regard it rather as the sum of an almost infinite number of small forces; so that we can subtract from or add to its strength within limits without bringing it out of the category of a "bond" or valency. For example, if the force employed in uniting two atoms together by means of a single bond be termed "F^2," then the quantity F will be negligible in comparison with the force of the single bond. But it is quite conceivable that this small force F would be sufficient to cause a difference of *reactivity* according as it were added to or subtracted from the force F^2. Thus the two forces expressed by $F^2 + F$ and $F^2 - F$ would not differ appreciably in their capacity for uniting two atoms, and certainly would not be so different as to allow the first atom to unite with two others; yet at the same time they would be sufficiently different to produce a change in reactivity of an atom attached to another by one or other of them.

From this point of view, investigations of the reactivities of certain atoms and groups in molecules are of the greatest importance. A considerable amount of work in this direction has already been carried[2] out; but a vast field lies open to research in this branch of the subject. With an increase in our knowledge of the factors which govern the reactive power of compounds must come, in the end, a modification of our structural formulæ.

We are now in a position, not, certainly, to forecast the character of the symbols which will replace our present ones,

[1] An interesting paper by Tschitschibabin (*J. pr. Chem.*, 1912, **86**, 381) on "The Valency of Carbon Atoms in so-called 'Unsaturated' Compounds" may be brought to the notice of the reader in this connection.

[2] See among others, Clarke, *Trans.*, 1911, **99**, 1432; 1912, **101**, 1788; Harper and Macbeth, *Trans.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824; Petrenko-Kritschenko, *J. pr. Chem.*, 1900, [2], **61**, 431; Petrenko-Kritschenko and Kantscheff, *Ber.*, 1906, **39**, 1452; Senter, *Trans.*, 1909, **95**, 1827; *ibid.*, 1910, **97**, 1623; Stewart, *Trans.*, 1905, **87**, 185, 410.

but to state clearly what functions these symbols will have to fulfil if they are to be regarded as satisfactory. They will have to cover the reactions which compounds undergo and to do this better than our present notation permits. They will have to indicate in some manner the reactivity of the compound, as distinct from the mere power of entering into reactions. And, finally, they will have to embody the knowledge of the intimate structure of molecules which we may in future obtain.

It is not to be expected that success will be attained at a stroke. Much more probably, there will be a good deal of fumbling and recasting to be gone through, just as there was before our present-day formulæ emerged from the melting-pot. Any suggestions, therefore, which tend towards the enlargement of our ideas of chemical constitution should be welcomed by those who have sufficient critical spirit to grasp the failure of our contemporary formulæ under the strain of modern investigation.

INDEX OF NAMES

INDEX

SUBJECTS

ERRATA.

P. 204. In the formula for aetiophyllin, the methyl and ethyl radicles attached to the top right-hand pyrrol nucleus should be replaced by hydrogen atoms.

P. 238. In the last formula on the page, COOH should be CHO.

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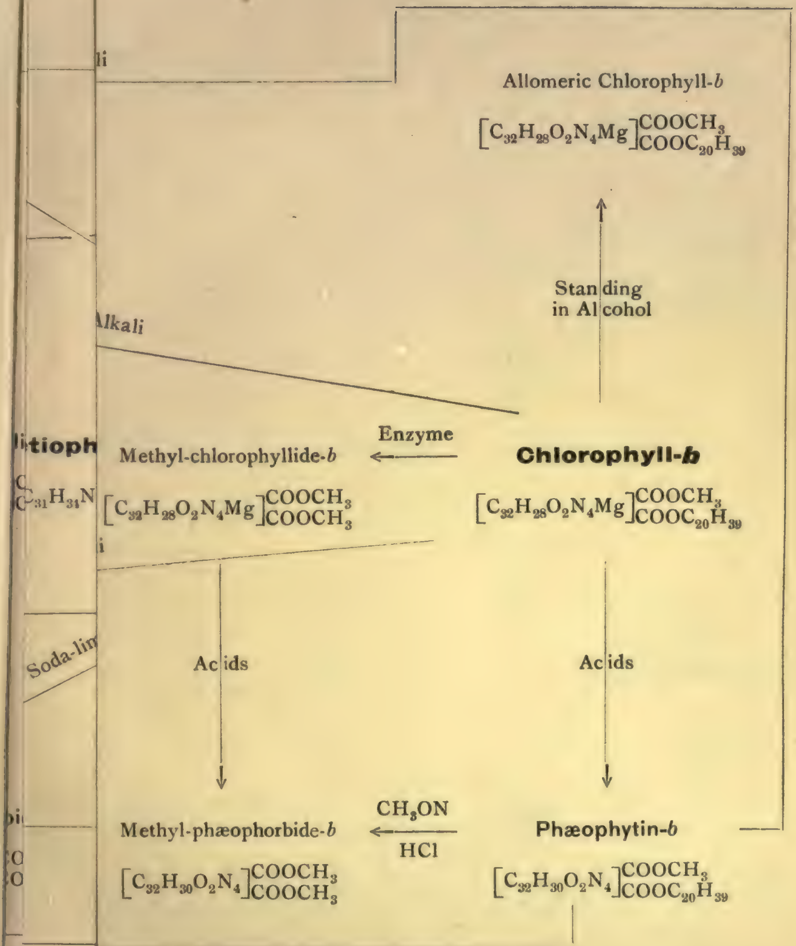


li
Allomeric Chlorophyll-b
$\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}$
Standing in Alcohol
Alkali
Enzyme
itioph
Methyl-chlorophyllide-b
$\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOCH_3\\COOCH_3\end{matrix}$
Chlorophyll-b
$\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}$
$C_{31}H_{31}N$
Soda-lin
Acids
Acids
CH_3ON
HCl
Methyl-phæophorbide-b
$\left[C_{32}H_{30}O_2N_4\right]\begin{matrix}COOCH_3\\COOCH_3\end{matrix}$
Phæophytin-b
$\left[C_{32}H_{30}O_2N_4\right]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}$

Dilute Alkali

Allomeric Chlorophyll-*a*

$\left[C_{32}H_{30}ON_4Mg\right]^{COOCH_3}_{COOC_{20}H_{39}}$

$\uparrow$ Standing in Alcohol

Chlorophyll-*a*

$\left[C_{32}H_{30}ON_4Mg\right]^{COOCH_3}_{COOC_{20}H_{39}}$ $\xrightarrow{\text{Enzyme}}$ Methyl Chlorophyllide-*a* $\left[C_{32}H_{30}ON_4Mg\right]^{COOCH_3}_{COOCH_3}$ $\xrightarrow{\text{Enzyme}}$ Chlo…

$\left[C_{32}H_{30}\ldots\right.$

With Acids $\downarrow$ $\uparrow$ CH_3MgI

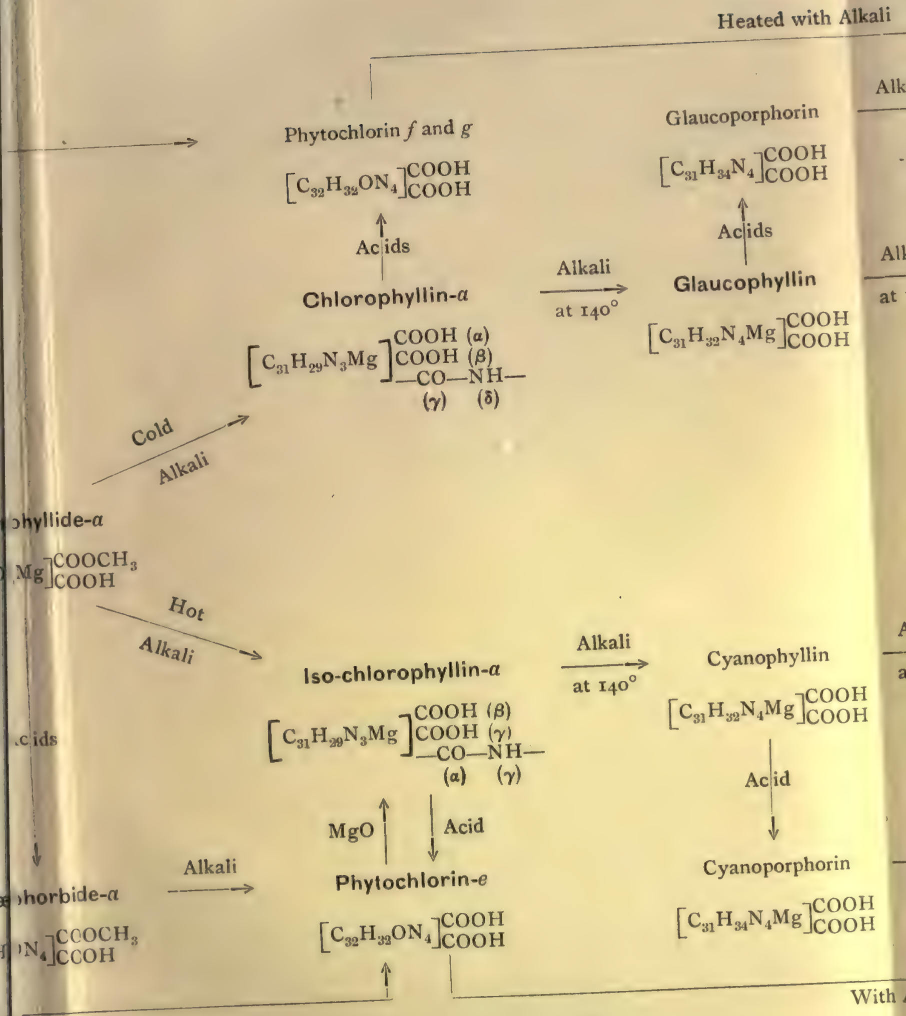
Acids $\downarrow$

Phæophytin-*a*

$\left[C_{32}H_{32}ON_4\right]^{COOCH_3}_{COOC_{20}H_{39}}$ $\xrightarrow[+\ HCl]{CH_3OH}$ Methyl Phæophorbide-*a* $\left[C_{32}H_{32}ON_4\right]^{COOCH_3}_{COOCH_3}$ $\xrightarrow[HCl]{\text{Conc.}}$ Ph…

$\left[C_{32}H\ldots\right.$

Alkali


Heated with Alkali
Phytochlorin f and g
[C32H32ON4]COOH COOH
Acids
Chlorophyllin-α
[C31H29N3Mg]COOH (α) COOH (β) —CO—NH— (γ) (δ)
Alkali at 140°
Glaucoporphorin
[C31H34N4]COOH COOH
Acids
Glaucophyllin
[C31H32N4Mg]COOH COOH
Cold Alkali
Mg]COOCH3 COOH
Hot Alkali
Iso-chlorophyllin-α
[C31H29N3Mg]COOH (β) COOH (γ) —CO—NH— (α) (γ)
Alkali at 140°
Cyanophyllin
[C31H32N4Mg]COOH COOH
Acid
Cyanoporphorin
[C31H34N4Mg]COOH COOH
MgO
Acid
Alkali
Phytochlorin-e
[C32H32ON4]COOH COOH
With

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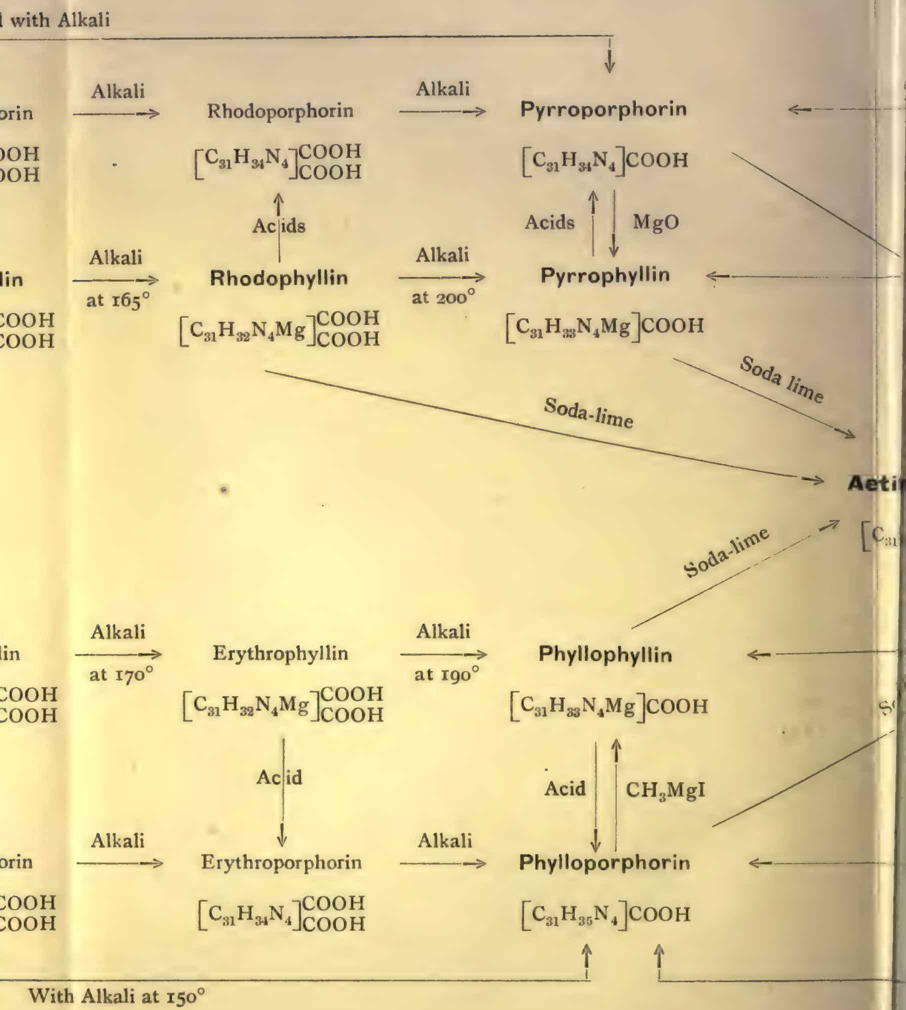
(WILLSTÄTTER, *Ber.*, 1914, 4



ILOROPHYLL

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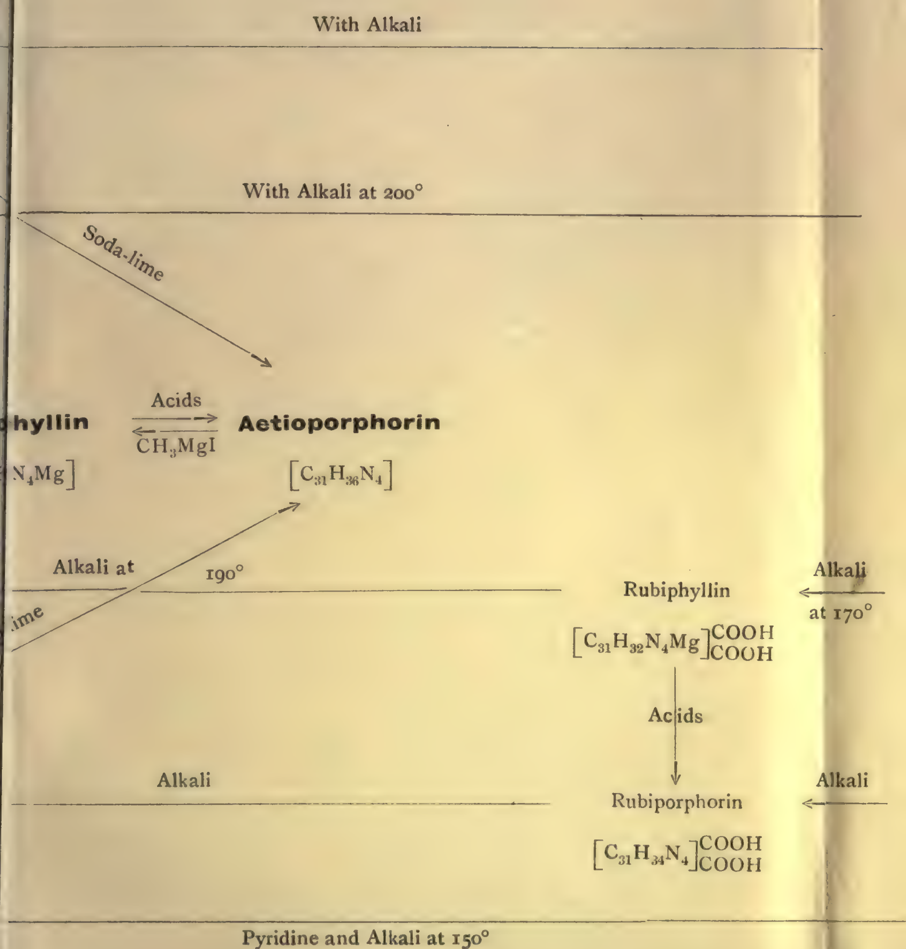
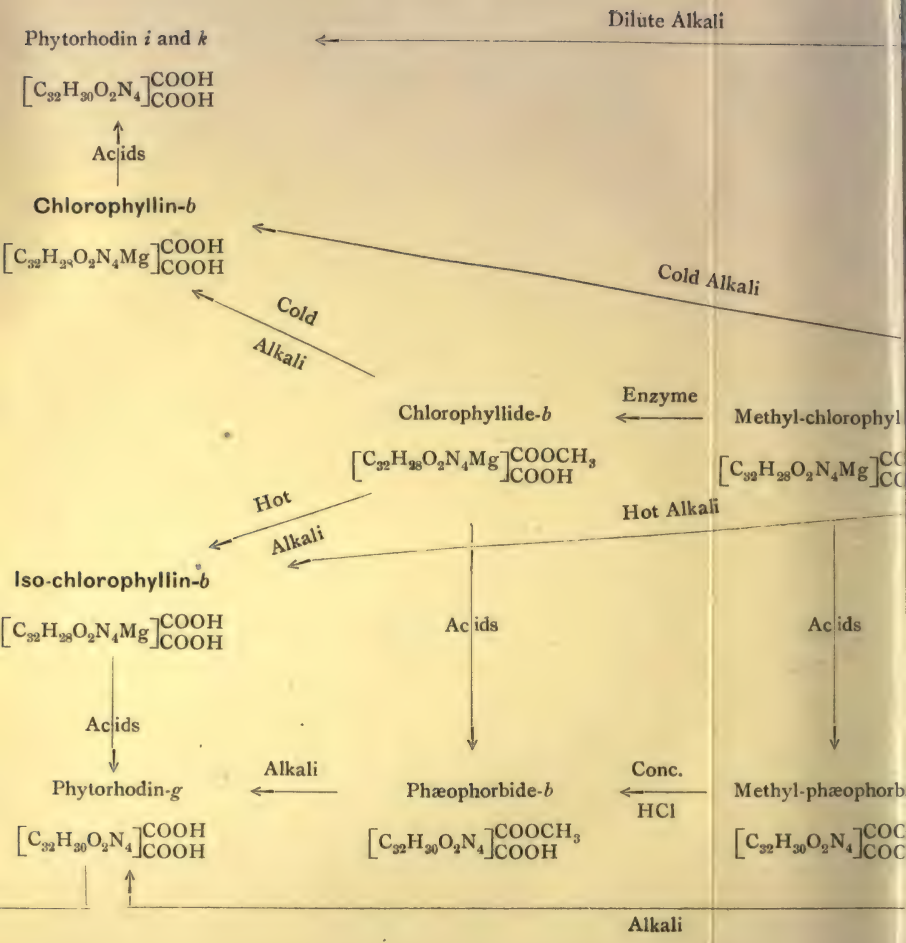



Dilute Alkali
Phytorhodin i and k
$\left[C_{32}H_{30}O_2N_4\right]\begin{matrix}COOH\\COOH\end{matrix}$
Acids
Chlorophyllin-b
$\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOH\\COOH\end{matrix}$
Cold Alkali
Cold Alkali
Chlorophyllide-b
$\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOCH_3\\COOH\end{matrix}$
Enzyme
Methyl-chlorophyl
$\left[C_{32}H_{28}O_2N_4Mg\right]$
Hot Alkali
Hot Alkali
Iso-chlorophyllin-b
$\left[C_{32}H_{28}O_2N_4Mg\right]\begin{matrix}COOH\\COOH\end{matrix}$
Acids
Acids
Acids
Alkali
Phytorhodin-g
$\left[C_{32}H_{30}O_2N_4\right]\begin{matrix}COOH\\COOH\end{matrix}$
Phæophorbide-b
$\left[C_{32}H_{30}O_2N_4\right]\begin{matrix}COOCH_3\\COOH\end{matrix}$
Conc. HCl
Methyl-phæophorb
$\left[C_{32}H_{30}O_2N_4\right]\begin{matrix}COC\\COC\end{matrix}$
Alkali

Allomeric Chlorophyll-*b*

$$\left[C_{32}H_{28}O_{2}N_{4}Mg\right]\begin{matrix}COOCH_{3}\\COOC_{20}H_{39}\end{matrix}$$

$$\uparrow \text{ Standing in Alcohol}$$

$$\overset{\text{Enzyme}}{\longleftarrow}$$

Chlorophyll-*b*

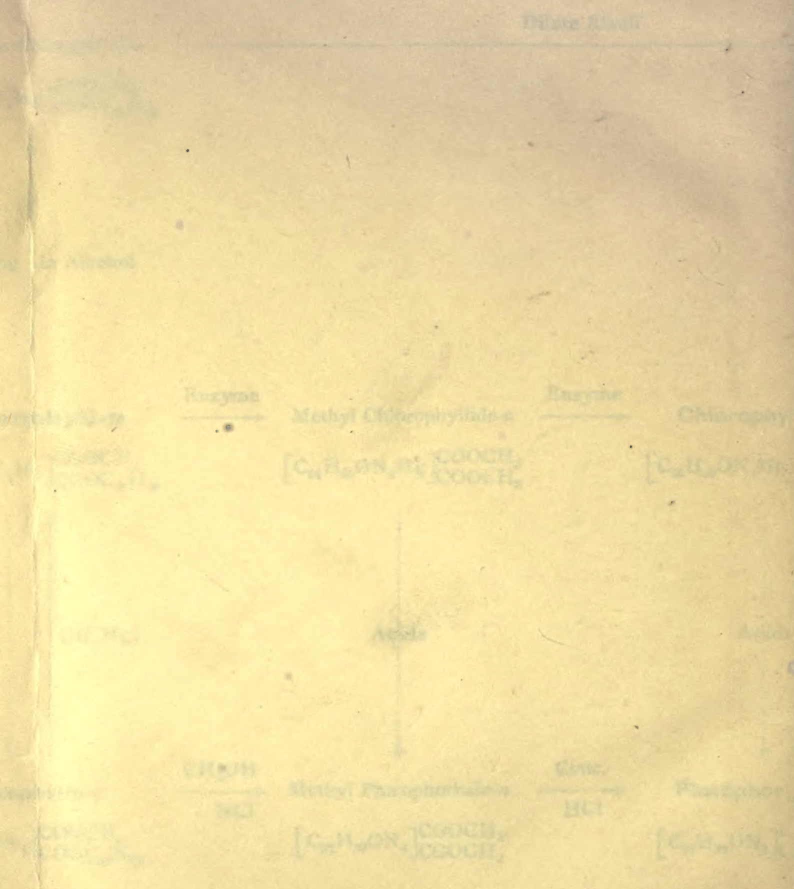
$$\left[C_{32}H_{28}O_{2}N_{4}Mg\right]\begin{matrix}COOCH_{3}\\COOC_{20}H_{39}\end{matrix}$$

$$\downarrow \text{ Acids}$$

$$\underset{HCl}{\overset{CH_{3}ON}{\longleftarrow}}$$

Phæophytin-*b*

$$\left[C_{32}H_{30}O_{2}N_{4}\right]\begin{matrix}COOCH_{3}\\COOC_{20}H_{39}\end{matrix}$$


Dilute Alkali
In Alcohol
Enzyme
Methyl Chlorophyllide a
Enzyme
Acids
Acids
Methyl Phaeophorbides
Conc.
HCl
HCl
Alkali